THE UNIVERSITY OF ALBERTA

PHENYL DICHLOROPHOSPHATE IN ORGANIC SYNTHESIS.

BY

JAMES M. NYANGULU

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SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND
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EDMONTON, ALBERTA

FALL, 1988

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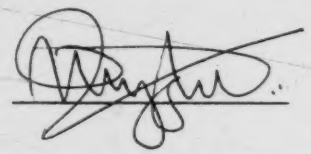

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

PHENYL DICHLOROPHOSPHATE IN ORGANIC SYNTHESIS

submitted by JAMES M. NYANGULU in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

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Date: OCT 05 1988

To

My parents, Ms. C. Nyangulu and the late Mr. P. J. Nyangulu,

my wife Christine and my son Kondwani.

Abstract

The first chapter of this thesis describes an efficient method for the mild oxidation of primary and secondary alcohols to their corresponding carbonyls, using phenyl dichlorophosphate as the dimethyl sulfoxide activator. The keto alcohol **7** was readily oxidized to the corresponding diketone **8** with a small amount of the chloro diketone **9** as a by-product. The secondary alcohol **16** was also converted to the ketone **17** without any epimerization. α-Methylbenzylamine, when treated with phenyl dichlorophosphate and dimethyl sulfoxide in the presence of triethylamine, gave acetophenone, presumably via the imine intermediate as shown in Scheme 5.

The second chapter describes a new facile method for the synthesis of β-chloroalkyl sulfides using dimethyl sulfoxide activated by phenyl dichlorophosphate or phosphorus oxychloride. The adduct **10** (Chapter 2) was readily formed from 1-octadecene. Under the same reaction conditions, styrene (**17**) unexpectedly gave the disulfide **18** (Chapter 2). α-Pinene (**22**) underwent a rearrangement reaction under the same reaction conditions to afford the chloride **23** (Chapter 2). A simple synthesis of carvone (**24**) from α-pinene via the chloride **23** is also described (Chapter 2).

Acknowledgements

I wish to take this opportunity to express my most sincere gratitude to Prof. H. J. Liu for his outstanding guidance and support during the course of this work and for his interest and assistance in the preparation of this thesis.

I would also like to thank the saints at Lusaka, Kabwata and Bible Baptist Church for their prayers and support. Very special thanks to my wife, Christine, for her invaluable encouragement and certainly to Kondwani for providing those happy moments even in those difficult days.

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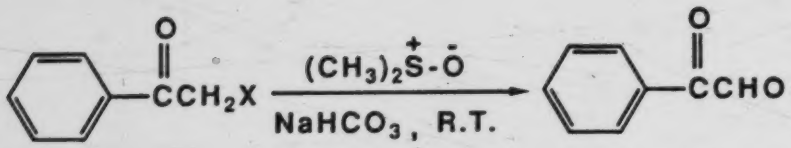
Chapter 1

Conversion of alcohols and amines to carbonyl compounds

Introduction

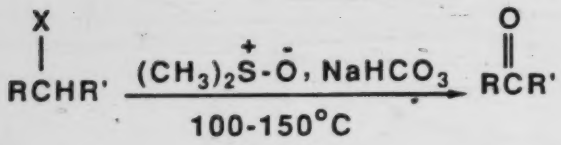
The reaction of dimethyl sulfoxide with electrophilic activators has proven highly useful in the mild oxidation of primary and secondary alcohols to their corresponding carbonyls.[1] The development of these procedures certainly provides an important addition to the tools of synthetic organic chemists.

The utilization of dimethyl sulfoxide as a reagent for the oxidation of primary and secondary alcohols stems in large part from the early work of Kornblum and coworkers[2]. In 1957 they observed that a variety of phenacyl halides could be oxidized to phenylglyoxals by dissolving them in dimethyl sulfoxide at room temperature in the presence of a base, such as sodium bicarbonate (Eq 1). Later, they were able to show that benzyl halides and many primary alkyl tosylates could also be converted to aldehydes in good yields (68-85%) by heating them at 100-150°C in dimethyl sulfoxide containing sodium bicarbonate[3] (Eq 2). From their observations, the nucleophilicity of the oxygen atom of dimethyl sulfoxide was clearly demonstrated. It was from this observation that a variety of procedures using dimethyl sulfoxide with various activators were subsequently developed. The work in this field has been extensively reviewed[1,4].



(Eq 1)

X= Cl, Br



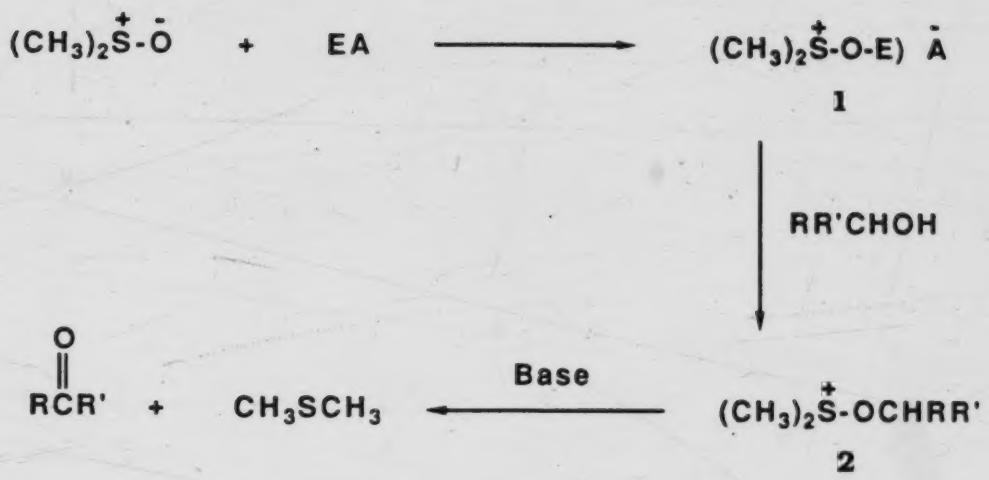
(Eq 2)

X= Cl, Br, Ts

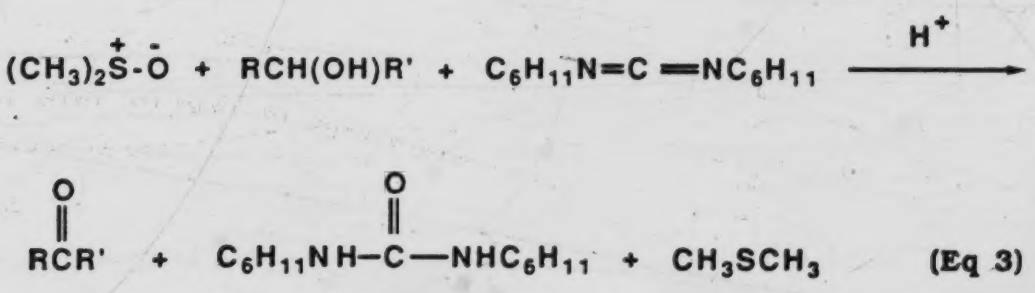
The successful use of dimethyl sulfoxide as an oxidant for the conversion of alcohols to their corresponding carbonyls requires initially, the activation of the dimethyl sulfoxide by a suitable electrophilic reagent as shown in Scheme 1. In principle, any compound which can react preferentially with the oxygen of the dimethyl sulfoxide can act as an activator in this oxidation procedure.

The reaction of dimethyl sulfoxide and an activator produces the intermediate **1** (Scheme 1). Subsequent attack by an alcohol on the electropositive sulfur atom with the departure of a leaving group leads to the formation of a dimethylalkoxysulfonium salt **2**. The reaction of the salt **2** with a base, usually triethylamine, forms dimethyl sulfide and the carbonyl product.

Scheme 1



In 1965, Pfitzner and Moffatt[5] developed an oxidation procedure in which dicyclohexylcarbodiimide (DCC) was used as the dimethyl sulfoxide activator. Although widely used in the oxidation of alcohols in the early years, extensive purification of the carbonyl product is necessary in order to remove the undesired urea produced as a by-product during the reaction (Eq 3).



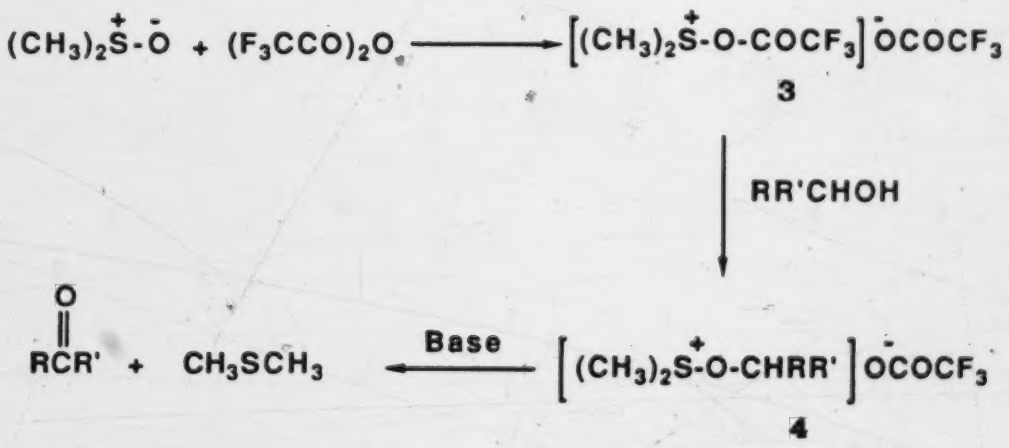
(Eq 3)

In a modification of the Pfitzner-Moffatt oxidation, Albright and Goldman[6] used acetic anhydride as the dimethyl sulfoxide activator. This modification procedure, which has been widely applied in organic synthesis, is normally carried out at room temperature, and the yields of carbonyl compounds are often comparable to those obtained by using dicyclohexylcarbodiimide and dimethyl sulfoxide[7]. The major drawbacks of the dimethyl sulfoxide/acetic anhydride procedure are the long reaction times (18-24 hr) and the frequent formation of substantial amounts of methylthiomethyl ethers as by-products. Acetates are also major by-products when unhindered alcohols are oxidized. For example, treatment of cholesterol with acetic anhydride and dimethyl sulfoxide in the presence of triethylamine gave the methylthiomethyl ether as the major product[8].

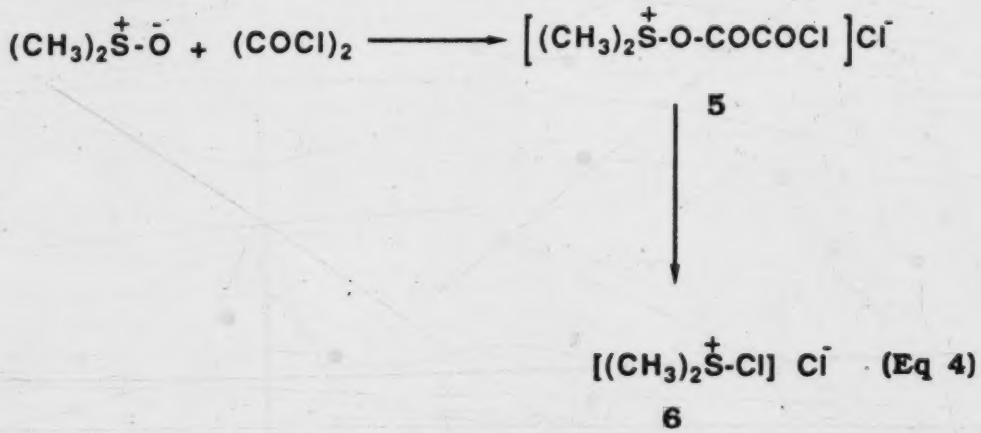
In 1975, Swern and coworkers[9] developed a procedure which was a modification of the Pfitzner-Moffatt oxidation in which trifluoroacetic anhydride is used as the dimethyl sulfoxide activator. The reaction between trifluoroacetic anhydride and dimethyl sulfoxide at room temperature in the absence of a solvent proceeds explosively. It is however possible to moderate the reaction by working at low temperatures in an inert solvent like dichloromethane[10]. Even under these conditions, dimethyl sulfoxide and trifluoroacetic anhydride react instantly and exothermically at -60°C in dichloromethane to produce presumably the dimethylsulfonium salt **3**. Reaction of an alcohol with the

intermediate **3** leads to the formation of the dimethylalkoxysulfonium salt **4**, which on treatment with base, usually triethylamine, yields the carbonyl product (Scheme 2). Several sets of conditions have been developed and are used depending on the nature of the substrate in order to achieve the best results[11,12]. The temperature at which the base is added appears to be very important and constitutes the major difference in two procedures that have been developed for trifluoroacetic anhydride. In one procedure, the base is added at -60°C and in the other it is added at room temperature. For the oxidation of some primary and small ring alcohols, different reaction conditions are employed [11].

Scheme 2



By far the most commonly used procedure is that developed by Swern and coworkers[12,13]. This is also a modification of the Pfitzner-Moffatt oxidation in which oxalyl chloride is used as the dimethyl sulfoxide activator. Oxalyl chloride and dimethyl sulfoxide react at -60°C in dichloromethane to give the chlorodimethylsulfonium intermediate **6**, obtained via the spontaneous loss of carbon dioxide and carbon monoxide from the intermediate **5**[12] (Eq 4). It is the intermediate **6** which reacts with an alcohol to form the dimethylalkoxysulfonium salt **4** which when treated with triethylamine gives the carbonyl product[12,14]. Corey *et al.*[15] have shown that the reactive intermediate **6** could also be prepared directly from chlorine and dimethyl sulfide. However, the operational simplicity and the high yields obtained when oxalyl chloride and dimethyl sulfoxide are used make this procedure especially advantageous.

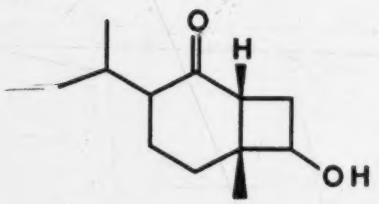


(Eq 4)

Several other reagents have been used to activate dimethyl sulfoxide and they include methanesulfonic anhydride[16], *p*-toluenesulfonyl chloride, *p*-toluenesulfonic anhydride, benzoyl chloride, cyanuric chloride, trifluoromethanesulfonic anhydride[17], sulfur trioxide/pyridine[18], phosphorus pentoxide, ethoxyacetylene[6], phosphorus trichloride[13], phosphoryl chloride, acetyl chloride, acetyl bromide and thionyl chloride[9]. Most of these reagents have not been found to be very useful due to the low yields obtained and long reaction times involved for many of them.

Towards the total synthesis of dendrobine in our laboratory, it was necessary to transform the keto alcohol **7** to the corresponding diketone **8**. Swern oxidation using oxalyl chloride[13] was attempted for this conversion. Surprisingly, the reaction gave an unexpected product which was characterized as the chloro diketone **9** apparently resulting from the concomitant α-chlorination of the existing cyclohexanone moiety. Presumably, complex **6** was involved as a source of positive chlorine[14]. Although this problem could be circumvented by using other dimethyl sulfoxide activators like acetic anhydride[6] or trifluoroacetic anhydride[9], the reaction was found to be rather slow when the former was used, while with the latter, the results were not highly reproducible. Moreover, in both cases, the yield of the desired diketone **8** was only modest. In order to improve the reaction, other possible activating agents were investigated.

Phosphorus-containing compounds are of particular interest mainly due to their high reactivity towards oxygen functionalities. As shown earlier, phosphorus oxychloride, phosphorus pentoxide and phosphorus trichloride have already been examined and found to be markedly inferior to oxalyl chloride and trifluoroacetic anhydride[13]. Upon examination of a series of other phosphorus-containing compounds which also included diphenyl chlorophosphate **11** and diethyl chlorophosphate **12**, phenyl dichlorophosphate **10** emerged as an efficient dimethyl sulfoxide activator.



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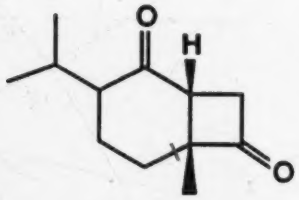

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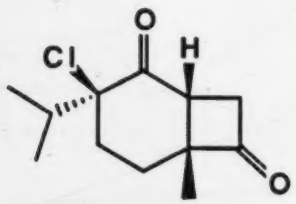

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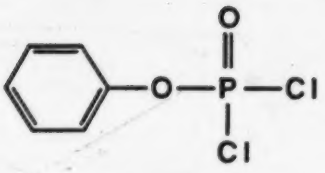

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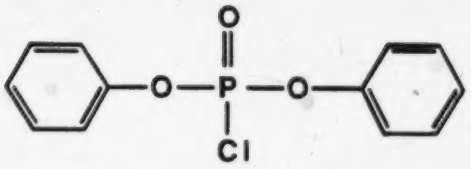

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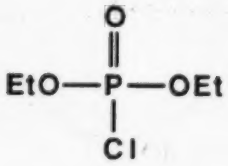

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During the course of our studies, the use of phenyl dichlorophosphate **10** in combination with dimethyl sulfoxide in the transformation of primary amines to their corresponding carbonyls was also investigated. From the preliminary results obtained which are also reported in this thesis, the procedure shows promise as an effective means for the transformation of benzylic amines to the corresponding carbonyls.

A variety of metal oxidizing reagents have been used including potassium permanganate[19], lead tetraacetate[20] and nickel (IV) oxide[21] in the oxidation of primary amines to carbonyls. The use of chloramine intermediates[22] and dehydrogenation with selenium reagents or via sulfinamides has also been demonstrated[23], although

the formation of the imines and their hydrolysis often requires elevated temperatures and strong acid.

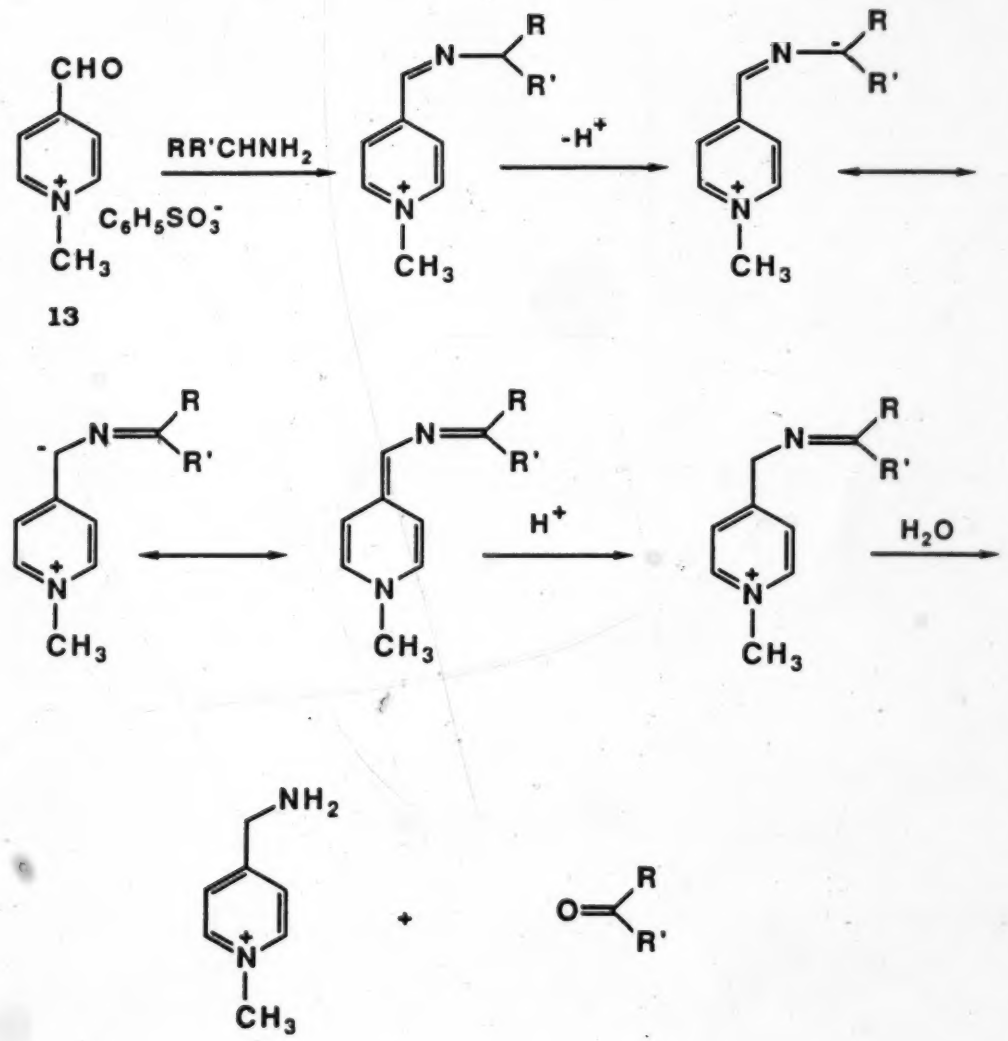
A number of transaminations have been developed that involve prototropic rearrangement and equilibration of Schiff base intermediates. Imines prepared from 3,5-di-*tert*-butyl-1,2-benzoquinone[24] have been used to afford ketones in high yields, although this method is not applicable to the preparation of aldehydes.

A recent example of the prototropic rearrangement method involves the formation of imines with pyridine-2-carboxaldehyde[25]. Deprotonation with lithium diisopropylamide afforded the resonance-stabilized anion which is subsequently protonated and hydrolysed to afford simple aldehydes and ketones in high yields. The major disadvantage of this process lies in the strong base required and its potential incompatibility with functional groups in more complex substrates.

In 1982, Rapoport *et al.*[26] showed that the 4-formyl-1-methylpyridinium salt **13** is a convenient reagent for the modification of amines to aldehydes and ketones. Rapoport's investigation was based on established transamination sequences of pyridoxal phosphate[27]. It is established that pyridoxal phosphate is exceptionally receptive to nucleophilic addition because of its highly polarized carbonyl group. The enzyme system responsible for this

process serves two fundamental functions. The first one is to control the protonation of the pyridine nitrogen and the second is to control the subsequent abstraction of an imine hydrogen, initiating prototropic rearrangement of the original Schiff base. As shown in Scheme 3, Rapoport's procedure involves imine formation, prototropic rearrangement and hydrolysis to the carbonyl product.

Scheme 3



Results and Discussion

As described earlier, it was necessary to convert the keto alcohol **7** to the diketone **8** in the course of studies on dendrobine in our laboratory. Unexpectedly, Swern oxidation using oxalyl chloride gave the chloro diketone **9** as the major product[14]. In an attempt to improve the yield of the desired diketone **8**, other dimethyl sulfoxide activators were tried. When acetic anhydride was used, the yield of the desired diketone **8** was very low and long reaction times were involved. With trifluoroacetic anhydride, the yield of the desired product was also low and the reaction was not highly reproducible.

During the course of our studies, a series of phosphorus-containing reagents which included phenyl dichlorophosphate **10**, diphenyl chlorophosphate **11** and diethyl chlorophosphate **12** were also examined. Of these reagents, phenyl dichlorophosphate **10** was found to be a highly efficient dimethyl sulfoxide activator in the conversion of alcohols to carbonyls. Phenyl dichlorophosphate (3 eq) was added to a stirred solution of dimethyl sulfoxide (5 eq) at -60°C. The reaction mixture was stirred for 10 min and the keto alcohol **7** (1 eq) added. Stirring was continued for 15 min and then triethylamine (5 eq) added. The reaction mixture was stirred at -60°C for 5 min and then allowed to warm up to room temperature. The reaction gave the desired diketone **8** in 77% yield with only a

small amount(10%) of the chloro diketone **9**. A small amount of starting material (12%) was also recovered. The diketone **8** displayed absorption bands in the ir spectrum at 1782 and 1700 cm^{-1} for the four- and six-membered ketones, respectively. The ^1H nmr spectrum showed a pair of doublets of doublets at δ3.48 (J=18, J'= 11.5 Hz) and δ3.00 (J=18, J'= 6 Hz). These signals and another doublet of doublets at δ2.74 (J=11.5, J= 6Hz) were assigned to the α-methylene protons of the four-membered ring ketone and the angular methine proton respectively. The mass spectrum exhibited a molecular ion peak at 194.1308 which is consistent with the chemical formula $C_{12}H_{18}O_2$. The small amount of the chloro diketone **9** obtained during the reaction displayed absorption bands in the ir spectrum at 1779 and 1709 cm^{-1} for the four- and six-membered ketones respectively. From the ^1H nmr, two doublets of doublets at δ3.64 (J=18, J'=11.5 Hz) and δ2.98 (J=18,J'=5.5 Hz) due to the α-methylene protons of the four-membered ring ketone were observed. The other doublet of doublets at δ3.14 (J=11.5, J'=5.5 Hz) was assigned to the angular methine proton. The mass spectrum showed molecular ion peaks at 228.0981 and 230.0897 corresponding to the chemical formula $C_{12}H_{17}O_2Cl$.

During the investigation, several sets of reaction conditions were attempted in order to arrive at the optimum conditions. The parameters that were investigated included the reaction temperature, the amounts of reagents necessary for maximum efficiency and the order of addition of the various reagents to the reaction mixture.

It was observed that when the oxidation was carried out at -60°C using the method described above, the reaction times were long and there was always a recovery of some starting material. On the other hand, when the reaction was performed at between -10° and -20°C, the starting material was completely consumed within 65 min to give the diketone **8** in 82% yield and a small amount of the chloro diketone **9**.

In another experiment, a modification in which the phosphate **10**, dimethyl sulfoxide and triethylamine were all mixed together at -10°C and then the keto alcohol **7** added, was attempted. Interestingly, within 45 min, the corresponding diketone **8** was produced in 84% yield with less than 10% of the chloro diketone **9**. This procedure is particularly advantageous because of its operational simplicity and the high yields of the carbonyl products.

The general procedure which was successfully applied to all the alcohols examined is described below. To a solution of dimethyl sulfoxide (5 eq) in dry dichloromethane at -10°C under an argon atmosphere, are added sequentially with stirring, phenyl dichlorophosphate (3 eq), triethylamine (5 eq) and a solution of the alcohol (1 eq) in dry dichloromethane. The reaction mixture is stirred at -10°C for 5 min, then allowed to slowly warm up to room temperature. The results obtained for the various alcohols examined are summarized in Table 1.

Table 1 : Oxidation of alcohols to their corresponding carbonyl compounds

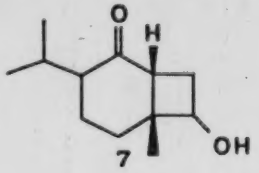
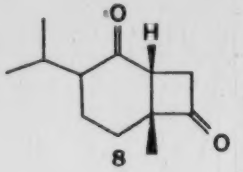
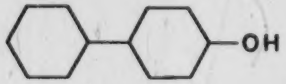
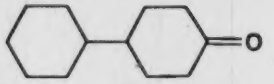
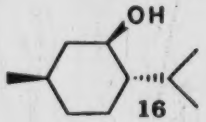
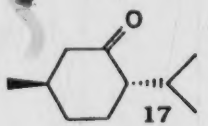
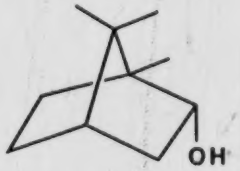
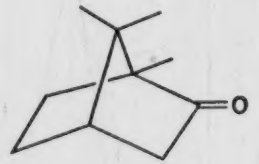
Entry	Substrate	Time(min)	Temp(°C)	Product	Yield(%)
1	 7	45	-10 → 20	 8	84
2	$CH_3(CH_2)_5CH(OH)CH_3$	35	-10 → 20	$CH_3(CH_2)_5COCH_3$	92
3		30	-10 → 20		90
4	$CH_3(CH_2)_{16}CH_2OH$ 14	45	-10 → 20	$CH_3(CH_2)_{16}CHO$ 15	77
5	 16	30	-10 → 20	 17	92
6		30	-10 → 20		81

Table 1 (cont'd)

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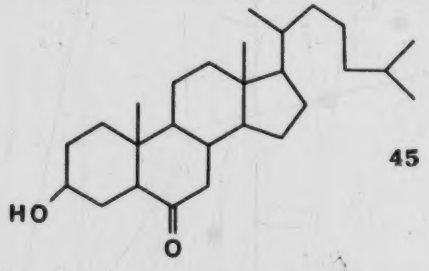
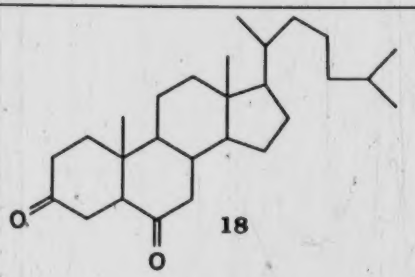
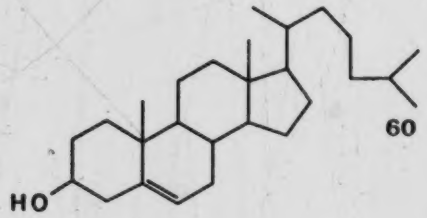
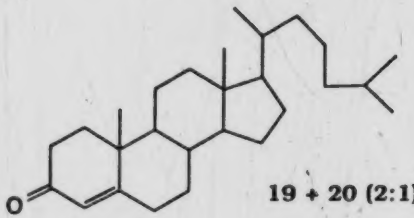
7		45	-10 → 20	 18	96
8		60	-10 → 20	 19 + 20 (2:1)	75

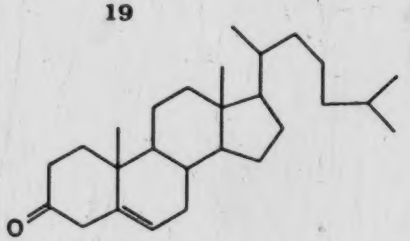

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Table 1 (cont'd)

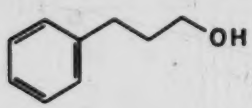
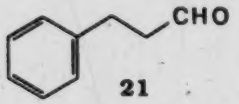
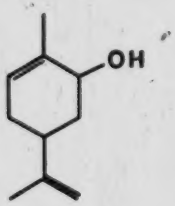
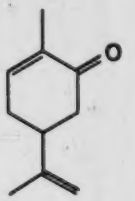
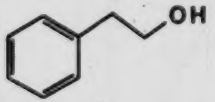
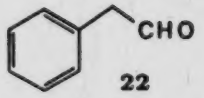
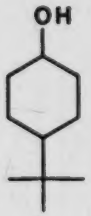
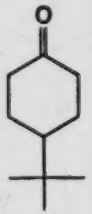
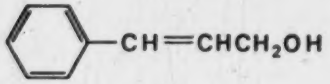
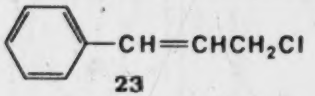
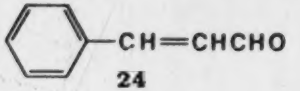
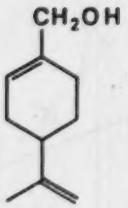
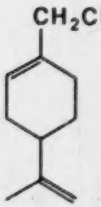
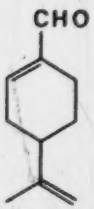
Entry	Substrate	Time(min)	Temp(°C)	Product	Yield(%)
9		30	-10 → 20	 21	80
10		45	-10 → 20		81
11		75	-10 → 20	 22	62
12		30	-10 → 20		94

Table 1 (cont'd)

Entry	Substrate	Time(min)	Temp(°C)	Product	Yield(%)
13		65	-10 → 20	 **23**	
				23 + 24 (~5:1)	**75**
				 **24**	
			-50 → 20	**23 + 24 (~1:2)**	**80**
14	 **25**	50	-10 → 20	 **26**	
				26 + 27 (~12:1)	**90**
				 **27**	
			-50 → 20	**26 + 27 (~1:1)**	**88**

It was also observed that when lesser amounts of the phosphate **10**, dimethyl sulfoxide or triethylamine were applied, the yield of the carbonyl product decreased, the reaction time was much longer and, in most instances, some starting material was recovered.

The long chain alcohol **14** (Entry 4) was readily converted to its corresponding aldehyde **15** in 77% yield using the phosphate **10**, dimethyl sulfoxide and triethylamine as described above. Interestingly, the attempted oxidation of the alcohol **14** with oxalyl chloride, dimethyl sulfoxide and triethylamine at -10°C using the procedure described above failed to give any detectable amount of the corresponding aldehyde **15** and a substantial amount of the starting material was recovered. On the other hand, the aldehyde **15** was formed in ca. 86% yield (determined by gas chromatography) when oxalyl chloride, dimethyl sulfoxide and the alcohol **14** were allowed to stir at -10°C for 15 min before adding triethylamine[12]. In a typical Swern oxidation, it is necessary to add the base at a particular temperature range after the reaction has proceeded for a period of time in order to achieve the best results.

Simple secondary alcohols were readily converted to their corresponding carbonyls in excellent yields. For example 2-octanol (Entry 2) and 4-cyclohexylcyclohexanol (Entry 3) were readily converted to their corresponding ketones in 92 and 90% yield respectively. Borneol (Entry 6) was also converted to camphor in 81% yield. When the secondary alcohol **16** (Entry 5) was treated

under similar conditions, the ketone **17** was produced as a single compound in 92% yield without any epimerization.

Of the steroidal alcohols examined, the reaction of cholestan-3-ol-6-one (Entry 7) proceeded smoothly to give the expected diketone **18** in 96% yield. This compound showed a broad absorption band in the ir spectrum at 1708 cm^{-1} for the two ketone functionalities. The mass spectrum showed a molecular ion peak at 400.3340 which is due to $C_{27}H_{44}O_2$. Under the same reaction conditions cholesterol (Entry 8) gave a mixture of two isomeric products in 2 to 1 ratio, determined from the ^1H nmr spectra in a total yield of 75%. The mixture showed strong absorption bands in the ir spectrum at 1680 cm^{-1} (conjugated ketone) and 1700 cm^{-1} (ketone). The major isomer **19** showed a sharp singlet at δ5.20 for the olefinic proton which was absent in the minor isomer **20**. The mass spectrum exhibited a molecular ion peak at 384.3379 confirming the chemical formula of $C_{27}H_{44}O$.

Several primary alcohols were also readily converted to the corresponding aldehydes in excellent yields. For example, the oxidation of 3-phenyl-1-propanol (Entry 9) proceeded smoothly in 30 minutes to produce the corresponding aldehyde **21** in 80% yield. The reaction of phenethyl alcohol (Entry 11) under similar conditions proceeded somewhat slower to give the aldehyde **22** in 62% yield. In all of these cases the structures of the carbonyl products were confirmed spectroscopically. Although the yield of the carbonyl compound **22** appears to be rather low, its yield is

much poorer when other activators are used. When oxalyl chloride was used, only 23% yield of the aldehyde **22** was obtained. In the case of trifluoroacetic anhydride the yield of the aldehyde **22** ranged from 32 to 50%.

It was observed that secondary allylic alcohols could also be readily transformed to their corresponding α,β-unsaturated ketones in high yields. For example, treatment of carveol (Entry 10) with the phosphate **10**, dimethyl sulfoxide and triethylamine at -10°C gave carvone in 81% yield. Treatment of primary allylic alcohols under similar reactions gave a mixture of two products. For example, the oxidation of cinnamyl alcohol (Entry 13) using the phosphate **10**, at -10°C gave a mixture of two products in an approximate ratio of 5 to 1. The major product **23** showed a doublet of doublets centred at δ4.25 (J=8, J'=2.5 Hz) in the ^{1}H nmr spectrum due to the methylene protons adjacent to the chlorine atom. Also present were a doublet at δ6.60 (J=15Hz) due to the olefinic proton on the benzylic carbon and a doublet of triplets centred at δ6.30 (J=16, J'=7 Hz) assigned to the other olefinic proton. This compound showed molecular ion peaks in the mass spectrum at 152.0392 and 154.0360 which are consistent with the chemical formula C_9H_9Cl. The expected aldehyde **24** was the minor product obtained and the structure was confirmed from spectral data which were found to be consistent with an authentic sample.

Similar results were observed when the primary allylic alcohol **25** was used a substrate under similar reaction conditions. The major product obtained was the chloro compound **26** in 83% yield, while the aldehyde **27** was obtained as the minor product in only 7% yield. The chloro-compound **26** showed a singlet in ^1H nmr at δ4.05 assigned to the methylene protons adjacent to the chlorine atom. A very broad singlet at δ5.85 was assigned to the olefinic proton in the cyclohexene ring system. The other broad singlet at δ4.75 was assigned to the terminal olefinic protons. Two molecular ion peaks in the mass spectrum were observed at 170.0863 and 172.0838 confirming the chemical formula $C_{10}H_{15}Cl$. The carbonyl product **27** exhibited an absorption band in the ir spectrum at 1680 cm^{-1} (conjugated aldehyde). The ^1H nmr spectrum showed a sharp singlet at δ9.45 for the aldehydic proton. A broad singlet due to the olefinic proton in the cyclohexene ring system was observed at δ6.85. Also present was a doublet centred at δ4.78 assigned two the two terminal olefinic protons. The molecular ion peak in the mass spectrum was observed at 150.1043 which is consistent with the chemical formula $C_{10}H_{14}O$.

The conversion of allylic or benzylic alcohols to halides under similar conditions has been reported in the literature. Corey and coworkers[28] showed that when N-chlorosuccinimide or chlorine and dimethyl sulfide are used to oxidize alcohols which can give stabilized cations, the oxidation process leading to the carbonyl product becomes only a minor pathway. They proposed that the

sulfoxonium intermediate **2** is relatively unstable and thus tends to form the corresponding chloride as the major product.

Swern *et al.*[19] also observed that the oxidation of cinnamyl alcohol using trifluoroacetic anhydride and dimethyl sulfoxide at room temperature did not produce any carbonyl product, but rather the alkyl trifluoroacetate **28** was obtained in 98% yield. It was proposed that the alkyl trifluoroacetate **28** forms as a result of the solvolysis of the allylic sulfoxonium salt which does not get oxidized (Eq 5).

$$(CH_3)_2\overset{+}{S}\text{-}\overset{-}{O} + (F_3CCO)_2O \longrightarrow [(CH_3)_2\overset{+}{S}\text{-}O\text{-}COCF_3]\ \overset{-}{O}COCF_3$$

$$\xrightarrow{PhCH{=}CHCH_2OH} PhCH{=}CHCH_2O\text{-}\overset{+}{S}(CH_3)_2\ \overset{-}{O}COCF_3$$

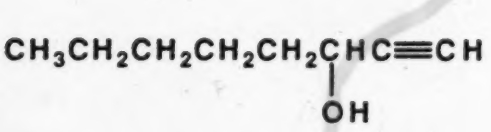
$$\xrightarrow{CF_3CO_2^-} PhCH{=}CHCH_2OCOCF_3 + (CH_3)_2\overset{+}{S}\text{-}\overset{-}{O} \quad \text{(Eq 5)}$$

28

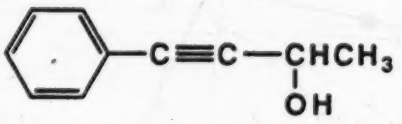
It was found that the formation of the chlorinated by-products could be supressed by performing the oxidations at much lower temperatures. When the oxidation of cinnamyl alcohol was carried

out at -50°C, a mixture of two products as before was obtained in an approximate ratio of 2 to 1 in favor of aldehyde **24**, in a total yield of 80%. Similarly, the alcohol **25** gave the aldehyde **27** in 48% yield when the oxidation was carried out at -50°C. The chloro compound **26** was obtained in 40% yield.

The oxidation of certain acetylenic alcohols using the phosphate **10**, dimethyl sulfoxide and triethylamine was unsuccessful. No isolatable carbonyl product was obtained when 1-octyn-3-ol (**29**) was used as the substrate. Under the same reaction conditions, the acetylenic alcohol **30** produced by the reaction of phenylacetylene and ethanal in the presence of butyllithium at -78°C also failed to produce any carbonyl product. Swern and coworkers[12] in their study did not get any carbonyl product from 1-octyn-3-ol (**29**) using either oxalyl chloride or trifluoroacetic anhydride.



29

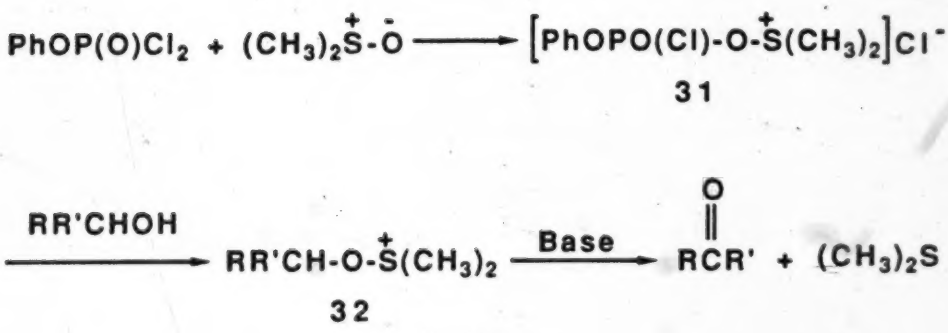


30

The proposed mechanism for the conversion of primary and secondary alcohols to corresponding aldehydes and ketones respectively using the phosphate **10** is outlined in Scheme 4. The reaction of dimethyl sulfoxide and phenyl dichlorophosphate at

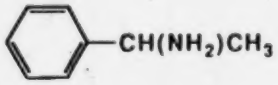
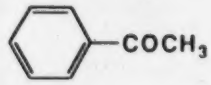
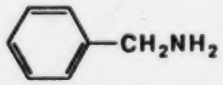
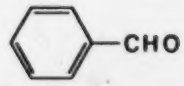
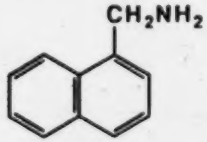
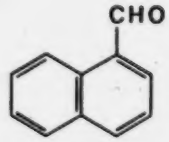
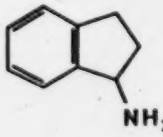
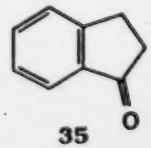
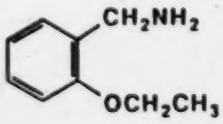
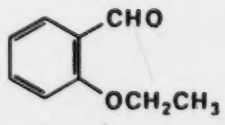
-10°C presumably leads to formation of complex **31**. The reaction of an alcohol with the complex **31** then leads to the formation of the dimethylalkoxysulfonium intermediate **32** which in the presence of base is converted to the carbonyl product.

Scheme 4

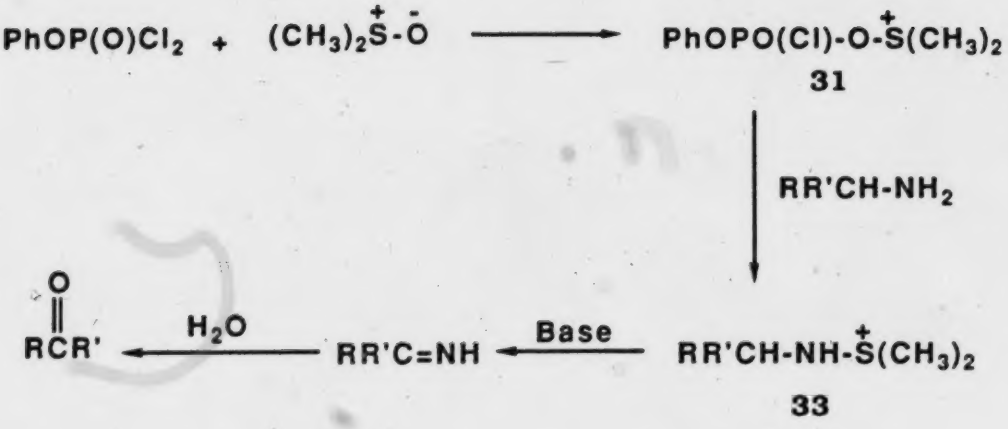


Based on this proposed mechanistic pathway, it is conceivable that carbonyl products from some amines can also be formed. As illustrated in Scheme 5, if the intermediate complex **31** reacts with an amine, it could presumably lead to the formation of the complex **33**. The treatment of complex **33** with a suitable base would then lead to the formation of an imine which upon acid hydrolysis is converted to the corresponding carbonyl product. A number of amines were examined in the hope of converting them to their corresponding carbonyl compounds. Results are summarized in Table 2.

Table 2 : Conversion of amines to their corresponding carbonyl compounds

Entry	Substrate	Time(h)	Temp(°C)	Product	Yield(%)
1		1.5	-10 → 20		80
2		1.5	-10 → 20		79
3		1.5	-10 → 20	 34	78
4		3.5	-10 → 20	 35	8
5		1.5	-10 → 20		76

Scheme 5



When α-methylbenzylamine was treated with 1.1 eq of phenyl dichlorophosphate, 2.2 eq of dimethyl sulfoxide and 5 eq of triethylamine and the reaction quenched with a saturated solution of oxalic acid, a small amount (<15%) of acetophenone was produced. In order to improve the yield of the carbonyl compound, the amounts of phenyl dichlorophosphate and dimethyl sulfoxide were increased to 3 eq and 6 eq respectively. The yield of acetophenone increased substantially to 80%.

Encouraged by the results obtained with α-methylbenzylamine, several other amino compounds were examined. In a typical reaction, a solution of dimethyl sulfoxide

(6 eq) and phenyl dichlorophosphate (5 eq) in freshly distilled dichloromethane is stirred at -10°C under an argon atmosphere for 5 min. The amino compound (1 eq) is then added and stirring continued for 15 min. Dry triethylamine (5 eq) is then added and stirring continued for 5 min. The temperature is then allowed to warm up slowly to room temperature. After an hour, a saturated solution of oxalic acid is added and stirring is continued at room temperature. It was observed in a separate experiment that the use of 1N HCl greatly enhanced the hydrolysis leading to the carbonyl product.

Benzylamine was successfully converted to benzaldehyde in 79% yield in 2.5 hr. Treatment of 1-naphthalenemethylamine under the same reaction conditions gave a 78% yield of the corresponding aldehyde **34**. 1-Aminoindan underwent the same transformation to give the corresponding ketone **35**, but only to the extent of 8%. Varying the amounts of phenyl dichlorophosphate and dimethyl did not bring about any improvement in the yield of the ketone **35**. The reaction of 2-ethoxybenzylamine with the phosphate **10** and dimethyl sulfoxide in the presence of triethylamine proceeded smoothly to give 2-ethoxybenzaldehyde in 76% yield

These results are only preliminary. More experiments to determine the optimum reaction conditions for the conversion of a variety of amino compounds to corresponding carbonyls are needed. Among the steps that may need to be undertaken in improving the yields of carbonyl products is the examination of the effect of using

bases other than triethylamine. It was observed that whereas benzylic amines were readily converted to carbonyl products, the conversion of simple aliphatic amines like cyclohexylamine and 2-aminooctane to corresponding carbonyl compounds was more difficult and it is likely that they require the use of a much stronger base, such as sodium hydride.

In conclusion, phenyl dichlorophosphate **10** has proved to be an efficient activator for dimethyl sulfoxide in the conversion of alcohols and some amino compounds to the corresponding carbonyls. In particular with respect to the alcohol oxidation its efficiency compares favourably with other commonly used activators such as dicyclohexylcarbodiimide, acetic anhydride, trifluoroacetic anhydride and oxalyl chloride. A broad synthetic utility of this reagent is expected in view of its high efficiency and operational simplicity.

Experimental

General

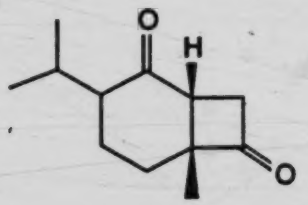
Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer. Unless otherwise stated, ir samples were run as thin films. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WH-200, WH-400, or AM-300 spectrometer and, except where stated, were obtained on solutions in deuteriochloroform using tetramethylsilane as internal reference. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad. Mass spectra (ms) were recorded on Kratos A.E.I. model MS-50 or MS-12 mass spectrometers. Concentration of solvent systems used in column chromatography are given by volumes, e.g. 20% ether in petroleum ether, means 20 parts of ether by volume to 80 parts of petroleum ether by volume.

Materials

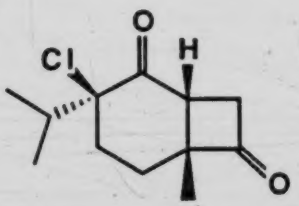
Dichloromethane used for reactions was freshly distilled over phosphorus pentoxide. Ether was distilled over lithium aluminum hydride. Triethylamine and ethyl acetate were freshly distilled over calcium hydride, as was dimethyl sulfoxide. Argon was passed

through a purification train of Fieser's solution[29], concentrated sulfuric acid and potassium hydroxide pellets. Flash chromatography developed by Still[30] was used routinely for purification and separation of product mixtures.

(1R*, 6R*)-3-Isopropyl-6-methylbicyclo[4.2.0]octane-2,7-dione (8) and (1R*, 3S*, 6R*)-3-Chloro-3-isopropyl-6-methylbicyclo-[4.2.0]octane-2,7-dione (9)



8



9

To a solution of dimethyl sulfoxide (0.35 mL, 5 mmol) in dichloromethane (10 mL) at -10°C under an argon atmosphere, were added sequentially with stirring phenyl dichlorophosphate (0.45 mL, 3 mmol), triethylamine (0.70 mL, 5 mmol) and a solution of the keto alcohol **6** (196 mg, 1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at -10°C for 5 min, then allowed to slowly warm up to room temperature. After 40 minutes, water (5 mL) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3x15 mL). The organic solution was washed with a saturated aqueous sodium chloride

solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The residue was subjected to flash column chromatography on silica gel. Elution with 20% ethyl acetate in petroleum ether afforded the chloro diketone **9** (23 mg, 10%): ir 1779 (four-membered C=O) and 1709 cm^{-1} (six-membered C=O); ^1H nmr δ3.64 (dd, 1H, J=18 Hz, J'=11.5 Hz, C-8H), 3.14 (dd, 1H, J=11.5 Hz, J'=5.5 Hz, C-1H), 2.98 (dd, 1H, J=18 Hz, J'=5.5 Hz, C-8H), 2.62 (septet, 1H, J=7 Hz, -C**H**$(CH_3)_2$), 1.37 (s, 3H, -C-C**H**$_3$), 1.12 and 0.9 (both d, 3H each, J=7 Hz each, -CH(C**H**$_3)_2$); ms M^+ 228.0924 and 230.0897 (calcd. for $C_{12}H_{17}ClO_2$: 228.0981 and 230.0888). *Anal.* Calcd. for $C_{12}H_{17}ClO_2$: C, 63.15; H, 7.51 Found: C, 63.24; H, 7.38. Further elution with the same solvent system afforded the diketone **8** (163 mg, 84% yield): ir 1782 (four-membered ring ketone) and 1700 cm^{-1} (six-membered ring ketone); ^1H nmr δ3.48; 3.42 (dd, 1/10H, J=18, J'=11.5 Hz; dd, 9/10H, J=18, J'=10.5 Hz, C-8H), 3.00; 3.26 (dd, 1/10H, J=18, J'=6 Hz; dd, 9/10H, J=18, J'=6 Hz, C-8H), 2.74; 2.76 (dd, 1/10H, J=11.5, J'=6 Hz; dd, 9/10H, J=10.5, J'=6 Hz, C-1H); ms M^+ 194.1306 (calcd. for $C_{12}H_{18}O_2$: 194.1307).

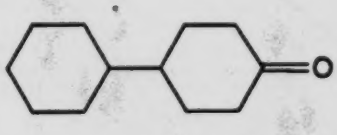
2-Octanone

$$CH_3(CH_2)_5COCH_3$$

A solution of dimethyl sulfoxide (0.35 mL, 5 mmol) in dry dichloromethane (5 mL) was cooled to -10°C under an argon

atmosphere. Phenyl dichlorophosphate (0.45 mL, 3 mmol), triethylamine (0.70 mL, 5 mmoL) and a solution of 2-octanol (130 mg, 1 mmol) in dichloromethane (5 mL) were then added sequentially with stirring. After stirring for 5 min at -10°C, the reaction mixture was allowed to slowly warm up to room temperature. After 30 min, water (5 mL) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3x10 mL). The organic solution was washed with saturated aqueous sodium chloride (15 mL), dried with magnesium sulfate, filtered and concentrated. The residue was subjected to flash column chromatography on silica gel. Elution with 25% diethyl ether in petroleum ether afforded 2-octanone (118 mg, 92% yield): ir 1712 cm^{-1} (ketone); ^1H nmr δ2.18 (s, 3H, CH_3CO-), 2.42 (t, 2H, J=7 Hz, -CH_2CH_2CO-), 0.90 (t, 3H, J=7 Hz, CH_3CH_2-) and 1.05 (m, 8H, $CH_3(CH_2)_4CH_2$-); ms M^+ 128.1200 (calcd. for $C_8H_{16}O$: 128.1201).

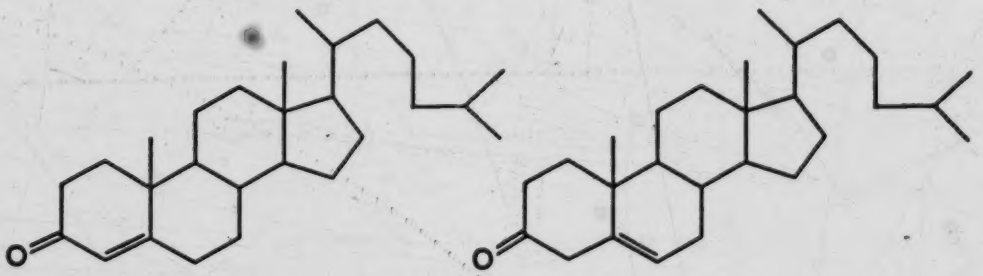
4-Cyclohexylcyclohexanone



To a solution of dimethyl sulfoxide (0.70 mL, 10 mmol) in freshly distilled dichloromethane (10 mL) were added with stirring phenyl dichlorophosphate (0.90 mL, 6 mmol), dry triethylamine (1.40 mL, 10 mmol) and a solution of 4-cyclohexylcyclohexanol

(365 mg, 2 mmol) in dry dichloromethane (5 mL). The mixture was allowed to stir at -10°C for 5 min and then allowed to warm up slowly to room temperature. After 25 min, water (5 mL) was added and stirring continued for another 5 min. The organic layer was separated and the aqueous layer extracted with dichloromethane (3x10 mL). The combined organic solution was washed with saturated sodium chloride solution (15 mL), dried with magnesium sulfate, filtered and concentrated. The resulting residue was subjected to flash column chromatography on silica gel. Elution with 30% diethyl ether in petroleum ether gave 4-cyclohexylcyclohexanone (325 mg, 90% yield): ir 1718 cm^{-1} (carbonyl); ^1H nmr δ2.25 (m, 4H, -CH_2COCH_2-), 1.05, and 1.45 (m, total 16H, cyclohexyl protons); ms M^+ 180.1513 (calcd. for $C_{12}H_{20}O$: 180.1515).

Cholest-4-en-3-one (19) and Cholest-5-en-3-one (20)



19 **20**

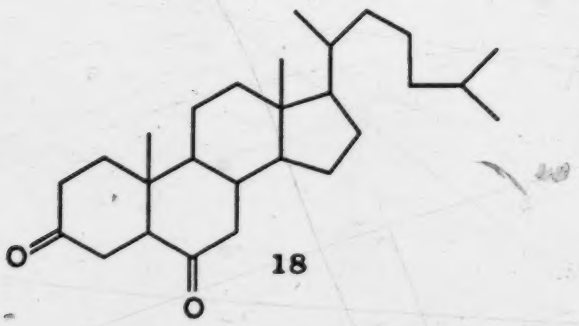
To a solution of phenyl dichlorophosphate (0.45 mL, 3 mmol) in freshly distilled dichloromethane (5 mL) at -10°C under an argon

atmosphere, were added with stirring dimethyl sulfoxide (0.35 mL, 5 mmol) in dry dichloromethane (5 mL), dry triethylamine (0.70 mL, 5 mmol) and a solution of cholesterol (386 mg, 1 mmol) in dichloromethane (3 mL). The reaction mixture was stirred for 5 min at -10°C and then allowed to warm up slowly to room temperature. After an hour, water (10 mL) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The combined organic solution was then washed with saturated sodium chloride solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The residue was subjected to flash column chromatography on silica gel. Elution with 20% ethyl acetate in petroleum ether gave the ketone **19** (192 mg, 50% yield): ir 1680 cm^{-1} (carbonyl); ^1H nmr δ5.20 (s,1H, =C**H**-), 0.68 (s 3H,-C**H**$_3$), 1.18 (s, 3H, -C**H**$_3$); ms M^+ 384.3379 (calcd. for $C_{27}H_{44}O$: 384.3392). Further elution with 25% ethyl acetate in petroleum ether afforded the compound **20** (96 mg, 25% yield): ir 1700 cm^{-1} (carbonyl); ^1H nmr δ4.20 (dd, 2H, J=6.5, J'=2.5 Hz -C**H**$_2$CH-), 0.68 (s, 3H, -C**H**$_3$); ms M^+ 384.3379 (calcd. for $C_{27}H_{44}O$: 384.3392).

Camphor

A solution of dimethyl sulfoxide (0.35 mL, 5 mmol) in freshly distilled dichloromethane (3 mL) was added to phenyl dichlorophosphate (0.45 mL, 3 mmol) in dry dichloromethane (3 mL) at -10°C under an argon atmosphere. Then were added with stirring, triethylamine (0.70 mL, 5 mmol) and borneol (154 mg, 1 mmol) dissolved in dichloromethane (3 mL). The reaction mixture was stirred for 5 min at -10°C and then allowed to slowly warm up to room temperature. After 25 min, water (5 mL) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The organic solution was then washed with saturated aqueous sodium chloride solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The residue was then subjected to flash chromatography on silica gel. Elution with 20% diethyl ether in petroleum ether afforded camphor (123 mg, 81% yield): ir 1742 cm^{-1} (ketone); ^1H nmr δ1.00 (s, 3H, -C**H**$_3$), 0.86 (s, 3H, -C**H**$_3$), 0.94 (s, 3H, -C**H**$_3$), 1.35 (m, 4H, -C**H**$_2$C**H**$_2$-) 2.38 (br, m, 2H, -CHC**H**$_2$CO-) and 1.95 (m, 1H, -CH$_2$C**H**CH$_2$-); ms M^+ 152.1199 (calcd. for $C_{10}H_{16}O$: 152.1201).

Cholestane-3,6-dione (18)

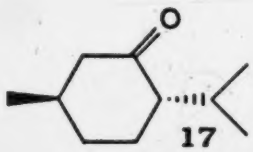


18

To a solution of dimethyl sulfoxide (0.35 mL, 5 mmol) in dry dichloromethane (3 mL) at -10°C under an argon atmosphere, were added sequentially with stirring, phenyl dichlorophosphate (0.45 mL, 3 mmol), triethylamine (0.70 mL, 5 mmol) and a solution of cholestan-3-ol-6-one (402 mg, 1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at -10°C for 5 min, then allowed to warm up to room temperature. After 40 min, the reaction mixture was quenched with water (10 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The organic solution was washed with saturated aqueous sodium chloride solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The crude material was chromatographed on silica gel, eluting with 20% ethyl acetate in petroleum ether to afford the diketone **18** (384 mg, 96% yield): ir 1708 cm^{-1} (ketone); ^1H nmr δ2.58 (m, 2H, -CH_2CO-), 0.68 (s, 3H,

-CH_3), 0.95 (s, 3H, -CH_3), 1.55 (m, 4H, -CH_2CH_2-); ms M^+ 400.3340 (calcd. for $C_{27}H_{44}O_2$: 400.3341).

Menthone (17)



17

A solution of dimethyl sulfoxide (0.35 mL, 5 mmol) in dry dichloromethane (5 mL) was cooled down to -10°C under an argon atmosphere. Phenyl dichlorophosphate (0.45 mL, 1 mmol), triethylamine (0.70 mL, 5 mmol) and a solution of the alcohol **16** (156 mg, 1 mmol) in dry dichloromethane (3 mL) were then added sequentially with stirring. The reaction mixture was stirred for 5 min and then allowed to slowly warm up to room temperature. After 25 min, water (10 mL) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3x15 mL). The organic solution was washed with saturated sodium chloride solution (15 mL), dried with magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with 20% diethyl ether in petroleum ether afforded the ketone **17** (142 mg, 92% yield): ir 1701 cm^{-1} (ketone); ^1H nmr δ0.86, 0.92, 1.02 (d, total 9H, J=7 Hz, -CH_3), 2.34, 2.38 (ddd, 2H, J=3, J'=4.5, J"=8 Hz, -C**H**CO-), 1.35 (m,

2H, $-CH_2CH_2-$), 1.85 (m, 2H, $-CH_2CH_2-$) and 2.15 (m, 2H, $-CH_2CO-$); ms M^+ 154.1360 (calcd. for $C_{10}H_{18}O$: 154.1358).

4-*tert*-Butylcyclohexanone

To a solution of phenyl dichlorophosphate (0.90 mL, 6 mmol) in dry dichloromethane (5 mL) at -10°C under an argon atmosphere, were added sequentially with stirring, dimethyl sulfoxide (0.70 mL, 10 mmol), dry triethylamine (1.40 mL, 10 mmol) and a solution of 4-*tert*-butylcyclohexanol (312 mg, 2 mmol) in dry dichloromethane. The reaction mixture was stirred at -10°C for 5 min, then allowed to slowly warm up to room temperature. After 25 min, the reaction was quenched with water (10 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The organic solution was washed with saturated sodium chloride solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 25% diethyl ether to

afford 4-*tert*-butylcyclohexanone (290 mg, 94% yield): ir 1719 cm^{-1} (ketone); ^1H nmr δ1.02 (s, total 6H, 2x $-CH_3$), 1.00 (s, 3H, $-CH_3$), 2.35 (m, 4H, $-CH_2COCH_2-$) and 1.45 (m, 1H, $-CH_2CHCH_2-$); ms M^+ 154.1360 (calcd. for $C_{10}H_{18}O$: 154.1358).

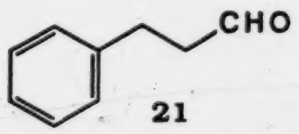
Octadecanal (15)

$$CH_3(CH_2)_{16}CHO$$
15

A solution of dimethyl sulfoxide (0.55 mL, 7.5 mmol) in dry dichloromethane (5 mL) was cooled down to -10°C under an argon atmosphere. Phenyl dichlorophosphate (0.70 mL, 4.5 mmol), dry triethylamine (1.05 mL, 7.5 mmol) and a solution of the long chain alcohol **14** (405 mg, 1.5 mmol) were then added sequentially with stirring. The reaction mixture was stirred for 5 min and then allowed to slowly warm up to room temperature. After 40 min, the reaction was quenched with water (10 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The organic solution was then washed with saturated sodium chloride solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with 25% ethyl acetate in petroleum ether afforded the aldehyde **15** (314 mg, 77% yield): ir 1711 (aldehyde), 2748 and 2849 cm^{-1} (aldehyde C-H); ^1H nmr δ9.75 (s, 1H, -CHO), 2.42 (t, 2H, J=6.5 Hz, $-CH_2CHO$), 0.85 (t, 3H,

J=6.5 Hz, CH_3CH_2-) and 1.25 (m, 30H, $CH_3(CH_2)_{15}CH_2$-); ms M^+ 268.2769 (calcd. for $C_{18}H_{36}O$: 268.2766).

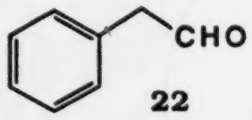
3-Phenylpropanal (21)



21

To a solution of dichlorophosphate (0.45 mL, 3 mmol) in dry dichloromethane (3 mL) at -10°C under an argon atmosphere were added dimethyl sulfoxide (0.35 mL, 5 mmol), triethylamine (0.70 mL, 5 mmol) and 3-phenyl-1-propanol (136 mg, 1 mmol) with stirring. The reaction mixture was stirred at -10°C for 5 min, then allowed to slowly warm up to room temperature. After 25 min, the reaction was quenched with water (10 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The organic solution was washed with aqueous saturated sodium chloride solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The resulting residue was chromatographed on silica gel. Elution with 15% ethyl acetate in petroleum ether afforded the aldehyde **21** (107 mg, 80% yield): ir 1701 (aldehyde), 2750, 2850 cm^{-1} (aldehyde C-H); ^1H nmr δ9.82 (s, 1H, -CHO), 2.95 (m, 2H, Ar-CH_2-), 2.80 (m, 2H, -CH_2CHO) and 7.25 (m, 5H, aromatic protons); ms M^+ 134.0733 (calcd. for $C_9H_{10}O$: 134.0732).

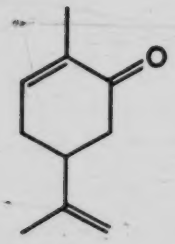
Phenylacetaldehyde (22)



22

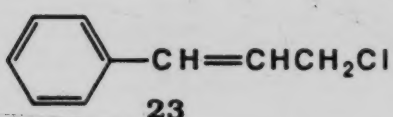
A solution of dimethyl sulfoxide (0.70 mL, 10 mmol) in dry dichloromethane (3 mL) was added to phenyl dichlorophosphate (0.90 mL, 6 mmol) in dichloromethane (3 mL) at -10°C under an argon atomosphere. Triethylamine (1.40 mL, 10 mmol) was then added dropwise with stirring followed by phenethyl alcohol (244 mg, 2 mmol). The reaction mixture was stirred for 10 min. After an hour, water (10 mL) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3x25 mL). The combined organic solution was then washed with saturated aqueous sodium chloride solution (25 mL), dried with magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with 15% ethyl acetate in petroleum ether afforded the aldehyde **22** (149 mg, 80% yield): ir. 1698 (aldehyde), 2748, 2849 cm^{-1} (aldehyde C-H); ^1H nmr δ9.70 (br, s, 1H, -C**H**O), 2.65 (br, s, 2H, -C**H**$_2$CHO) and 7.32 (br, s, 5H, aromatic protons); ms M^+ 120.0576 (calcd. for C_9H_8O: 120.0575).

Carvone

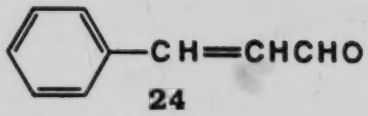


To a solution of phenyl dichlorophosphate (0.45 mL, 3 mmol) in freshly distilled dichloromethane (3 mL) at -10°C under an argon atmosphere, was added dimethyl sulfoxide (0.35 mL, 5 mmol) in dry dichloromethane (3 mL). After stirring for 2 min, triethylamine (0.70 mL, 5 mmol) was added dropwise followed by a solution of carveol (152 mg, 1 mmol) in dichloromethane (2 mL). The reaction mixture was stirred for 5 min at -10°C and then allowed to warm up slowly to room temperature. After stirring for 45 min, water (10 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The combined organic solution was washed with saturated sodium chloride solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The resulting residue was chromatographed on silica gel. Elution with 25% diethyl ether in petroleum ether gave carvone (122 mg, 81% yield): ir 1673 cm^{-1} (conjugated ketone); ^1H nmr δ6.75 (m, 1H, =C**H**-), 4.75 (br, s, 1H, =C**H**H), 4.82 (br, s, 1H,=CH**H**), 1.80 (br, s, 3H, -C**H**$_3$) and 1.75 (br, s, 3H, -C**H**$_3$); ms M^+ 150.1042 (calcd. for $C_{10}H_{14}O$: 150.1045).

Oxidation of *trans*-Cinnamyl alcohol at -10°C



23



24

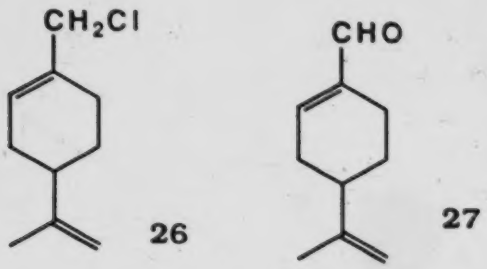
To a solution of phenyl dichlorophosphate (0.45 mL, 3 mmol) in dry dichloromethane (3 mL) at 10°C under an argon atmosphere, were added sequentially with stirring, dimethyl sulfoxide (0.35 mL, 5 mmol), triethylamine (0.70 mL, 5 mmol) and a solution of *trans*-cinnamyl alcohol (134 mg, 1 mmol) in dichloromethane (3 mL). The reaction mixture was stirred for 5 min at -10°C and then allowed to slowly warm up to room temperature. After stirring for an hour, the reaction was quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3x20 mL). The organic solution was washed with saturated sodium chloride solution (25 mL), dried with magnesium sulfate, filtered and concentrated. The resulting residue was subjected to flash chromatography on silica gel. Elution with 20% ethyl acetate in petroleum ether afforded the aldehyde **24** (16 mg, 12% yield): ir 1685 (conjugated aldehyde), 2747 and 2848 cm^{-1} (aldehyde C-H); ^1H nmr δ9.75 (br, s, 1H, -C**H**O), 6.60 (d, 1H, J=15 Hz, =C**H**-CHO) and 6.75 (d, 1H, J=15 Hz, Ar-C**H**=); ms M^+ 132.0570 (calcd. for C_9H_8O: 132.0571). Further elution with the same solvent system afforded the chloro compound **23** (96 mg,

63% yield): ir 3010 and 3020 cm^{-1} (=C-H); ^1H nmr δ4.25 (dd, 2H, J=8, J'=2.5 Hz, -CH_2Cl), 6.60 (d, 1H, J=15 Hz, Ar-CH=) and 6.30 (dt, 1H, J=15, J'=7 Hz, =$CHCH_2$-); ms M^+ 152.0392 and 154.0360 (calcd. for C_9H_9Cl: 152.0394 and 154.0364).

Oxidation of *trans*-Cinnamyl alcohol at -50°C

Phenyl dichlorophosphate (0.45 ml, 3 mmol) was added to a solution of dimethyl sulfoxide (0.35 mL, 5 mmol) in dichloromethane (3 mL) at -50°C under an argon atmosphere and the mixture was stirred for 5 min. Triethylamine (0.70 mL, 5 mmol) and a solution of *trans*-cinnamyl alcohol (134 mg, 1 mmol) in dichloromethane (2 mL) were added with stirring. The reaction mixture was stirred at -50°C for 30 min and then allowed to slowly warm up to room temperature. After 30 min the reaction was quenched with water (10 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3x25 mL). The combined organic solution was then washed with saturated sodium chloride solution (25 mL), dried with magnesium sulfate, filtered and concentrated. The residue was then purified by column chromatography using 20% ethyl acetate in petroleum ether to afford the aldehyde **24** (70 mg, 53% yield). Further elution wih the same solvent system gave the chloro compound **23** (41 mg, 27% yield).

Oxidation of Perillyl alcohol (25) at -10°C



26 27

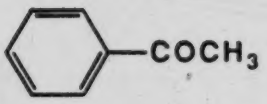
A solution of dimethyl sulfoxide (0.35 mL, 5 mmol) in dichloromethane (2 mL) was added to a solution of phenyl dichlorophosphate (0.45 mL, 3 mmol) in dichloromethane at -10°C under an argon atmosphere. After stirring for 2 min, triethylamine (0.70 mL, 5 mmol) and perillyl alcohol **25** (152 mg, 1 mmol) were then added. The reaction mixture was stirred at -10°C for 5 min and then allowed to slowly warm up to room temperature. After 45 min, water (10 mL) was added and the aqueous layer was extracted with additional dichloromethane (3x20 mL). The combined organic extracts were washed with saturated brine solution, dried over magnesium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with 5% ethyl acetate gave the aldehyde **27** (11 mg, 7% yield): ir 1680 (conjugated aldehyde), 2749, 2852 cm^{-1} (aldehyde C-H); ^1H nmr δ9.45 (s, 1H, -**CH**O), 6.85 (m, 1H, =**CH**-), 4.75 (br, s, 1H, =**CH**H), 4.82 (br, s, 1H, =**CH**H) and 1.78 (s, 3H, -**CH**$_3$); ms M^+ 150.1043 (calcd. for $C_{10}H_{14}O$:

150.1045). Further elution with 5% ethyl acetate in petroleum ether afforded the chloro compound **26** (141 mg, 83% yield): ir 3020 cm^{-1} (=C-H); ^1H nmr δ4.05 (s, 2H, $-CH_2Cl$), 5.85 (br, s, 1H, $=CH-$), 4.75 (m, 2H, $=CH_2$), 1.75 (s, 3H, $-CH_3$) and 2.20 (m, 4H, $-CH_2CH_2-$); ms M^+ 170.0863 and 172.0838 (calcd. for $C_{10}H_{15}Cl$: 170.0864 and 172.0834). *Anal.* Calcd. for $C_{10}H_{15}Cl$: C, 70.59, H, 8.82; Found C, 70.52, H, 8.94.

Oxidation of Perillyl alcohol (25) at -50°C

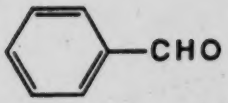
A solution of dimethyl sulfoxide (0.35 mL, 5 mmol) in dichloromethane (2 mL) was added to a solution of phenyl dichlorophosphate (0.45 mL, 3 mmol) in dichloromethane at -50°C under an argon atmosphere. The reaction mixture was stirred at -50°C for 5 min and then triethylamine (0.70 mL, 5 mmol) and perillyl alcohol **25** (152 mg, 1 mmol) were added. After 30 min at -50°C, the reaction mixture was allowed to warm up to room temperature. After stirring for 25 min, water (20 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x20 mL) and the combined organic extracts dried with magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography, eluting with 5% ethyl acetate in petroleum ether to afford the aldehyde **27** (72 mg, 48% yield). Further elution with the same solvent system gave the chloro compound **26** (68 mg, 40% yield).

Acetophenone



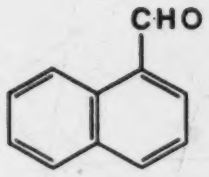
To a solution of dichloromethane (3 mL) and dimethyl sulfoxide (0.42 mL, 6 mmol) at -10°C under an argon atosmphere, was added phenyl dichlorophosphate (0.45 mL, 3 mmol) dropwise with stirring. 1-Phenylethylamine (121 mg, 1 mmol) was added dropwise after 5 min and stirring continued for 15 min after which triethylamine (0.70 mL, 5 mmol) was added. The reaction mixture was stirred at -10°C for 5 min and then allowed to slowly warm up to room temperature. After an hour, the reaction was quenched with aqueous saturated oxalic acid. After stirring for half an hour, the organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The combined organic solution was dried with magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel using 15% diethyl ether in petroleum ether to give acetophenone (96 mg, 80% yield): ir 1695 cm^{-1} (ketone); ^1H nmr δ2.58 (s, 3H, CH_3CO-) and 7.75 (m, 5H, aromatic protons); ms M^+ 120.0574 (calcd. for C_8H_8O: 120.0575).

Benzaldehyde



A solution of dimethyl sulfoxide (0.42 mL, 6 mmol) and dichloromethane (3 mL) was added to phenyl dichlorophosphate (0.45 mL, 3 mmol) in dichloromethane at -10°C under an argon atmosphere. After stirring for 5 min, benzylamine (107 mg, 1 mmol) was added and stirring was continued for 15 min after which triethylamine (0.70 mL, 5 mmol) was added. The reaction mixture was stirred for 5 min at -10°C and then allowed to warm up slowly to room temperature. After an hour, aqueous saturated oxalic acid was added. After stirring for an hour, the organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The combined organic extracts were dried, filtered and concentrated. The residue was purified by column chromatography using 10% ethyl acetate in petroleum ether to give benzaldehyde (84 mg, 79% yield): ir 1708 cm^{-1} (aldehyde); ^1H nmr δ9.88 (s, 1H, -CHO) and 7.45 (m, 5H, aromatic protons); ms M^+ 106.0418 (calcd. for C_7H_6O: 106.0418).

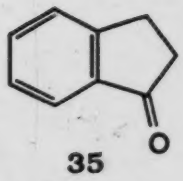
1-Naphthaldehyde (34)



34

Dimethyl sulfoxide (0.42 mL, 6 mmol) was added dropwise to a solution of dichloromethane (3 mL) and phenyl dichlorophosphate (0.45 mL, 3 mmol) at -10°C under an atmosphere of argon. 1-Naphthalenemethylamine (157 mg, 1 mmol) was added and stirring continued for 15 min. Triethylamine (0.70 mL, 5 mmol) was then added dropwise with stirring. The reaction mixture was stirred at -10°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, an aqueous saturated solution of oxalic acid (20 mL) was added and stirring continued for another hour. The organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The combined organic solution was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel eluting with 10% ethyl acetate in petroleum ether to give the aldehyde **34** (122 mg, 78% yield): ir 1695 cm^{-1} (aldehyde); ^1H nmr δ9.18 (s 1H, -CHO) and 7.50 (m, 7H, aromatic protons); ms M^+ 156.0575 (calcd. for $C_{11}H_8O$: 156.0575).

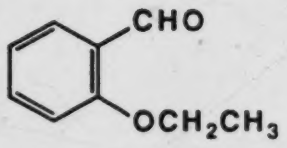
1-Indanone (35)



35

A solution of phenyl dichlorophosphate (0.45 mL, 3 mmol) in dry dichloromethane (2 mL) was added to dimethyl sulfoxide (0.42 mL, 6 mmol) in dichloromethane (3 mL) with stirring at -10°C under an argon atmosphere. 1-Aminoindan (132 mg, 1 mmol) was then added and the reaction mixture stirred for 15 min. Triethylamine (0.70 mL, 5 mmol) was added and the mixture was stirred at -10°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, an aqueous saturated solution of oxalic acid (20 mL) was added. After stirring for 2 hours, the organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography using 15% ethyl acetate in petroleum ether to afford the ketone **35** (11 mg, 8% yield): ir 1712 cm^{-1} (ketone); ^1H nmr δ7.50 (m, 4H, aromatic protons), 3.15 (t, 2H, J=5 Hz -CH_2CO-) and 2.68 (ddd, 2H, J=4, J'=8, J"=12 Hz, -CH_2CH_2CO-); ms M^+ 132.0575 (calcd. for C_9H_8O: 132.0575).

2-Ethoxybenzaldehyde



Dimethyl sulfoxide (0.42 mL, 6 mmol) was added dropwise to a solution of dichloromethane (3 mL) and phenyl dichlorophosphate (0.45 mL, 3 mmol) at -10°C under an argon atmosphere. 2-Ethoxybenzylamine (151 mg, 1 mmol) was added and stirring continued for 15 min. Triethylamine (0.70 mL, 5 mmol) was then added dropwise. The reaction mixture was stirred at -10°C for 5 min and then allowed to slowly warm up to room temperature. After stirring for 45 min, an aqueous saturated solution of oxalic acid (20 mL) was added and stirring continued for another 30 min. The organic layer was separated and the aqueous layer extracted with dichloromethane (3x20 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 15% ethyl acetate in petroleum ether to give 2-ethoxybenzaldehyde (114 mg, 76% yield): ir 1684 (aldehyde), 2859, 2750 cm^{-1} (aldehyde C-H); ^1H nmr δ10.5 (s, 1H, -C**H**O), 4.20 (q, 2H, J=7 Hz, -OC**H**$_2$CH$_3$), 1.50 (t, 3H, J=7 Hz, -OCH$_2$C**H**$_3$), 7.80 (m, 1H, aromatic H), 7.50 (m, 1H, aromatic H) and 7.00 (m, 2H, aromatic protons); ms M^+ 150.0679 (calcd. for $C_9H_{10}O_2$: 150.0681).

Chapter 2

Transformation of olefins to β-chloroalkyl sulfides

Introduction

The reaction between various sulfenyl chlorides and unsaturated compounds has for many years received considerable attention from organic chemists[31]. This reaction is of particular interest because it constitutes a convenient method for the synthesis of various β-chloroalkyl sulfides which are useful synthetic intermediates. Certain compounds of this family have been shown to possess antifungal and antibacterial properties[31,32].

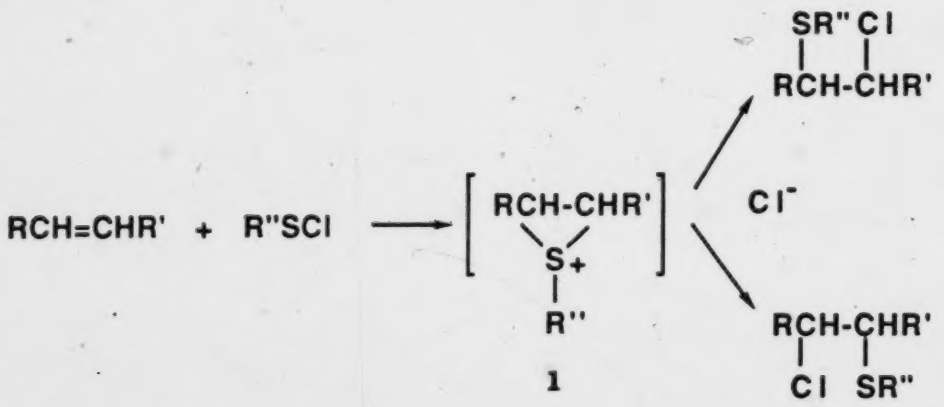
The addition of sulfenyl chlorides to olefins was first reported by Lecher and coworkers[33] in 1925. The study on sulfenyl chloride addition reactions was initiated in large part due to an observation made by Rathke[34] in 1870. Rathke reported the iodine-catalyzed chlorination of carbon disulfide leading to trichloromethanesulfenyl chloride, which is the longest-known sulfenyl chloride (Eq 1).

$$CS_2 \xrightarrow{Cl_2 / I_2 \ \ catalyst} Cl_3C\text{-}SCl + S_2Cl_2 \qquad \text{(Eq. 1)}$$

The sulfenyl chloride molecule could, in theory, react as a source of electrophilic sulfur or chlorine or as a source of free radicals by homolytic cleavage. Two of these possibilities, the occurence of electrophilic sulfur as well as that of free radicals, have been recognized to date[35]. Kharasch and Buess[36] in 1950 reported

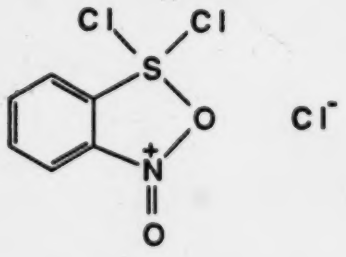
that, based on the results obtained from their studies, there was no evidence that a sulfenyl chloride could become a source of chloronium ions. According to Mueller[35], the almost exclusive *trans*-stereospecific addition observed with *cis*- and *trans*-2-butenes as well as with norbornene stands as additional support in favour of the episulfonium intermediate ion **1**.

Scheme 1

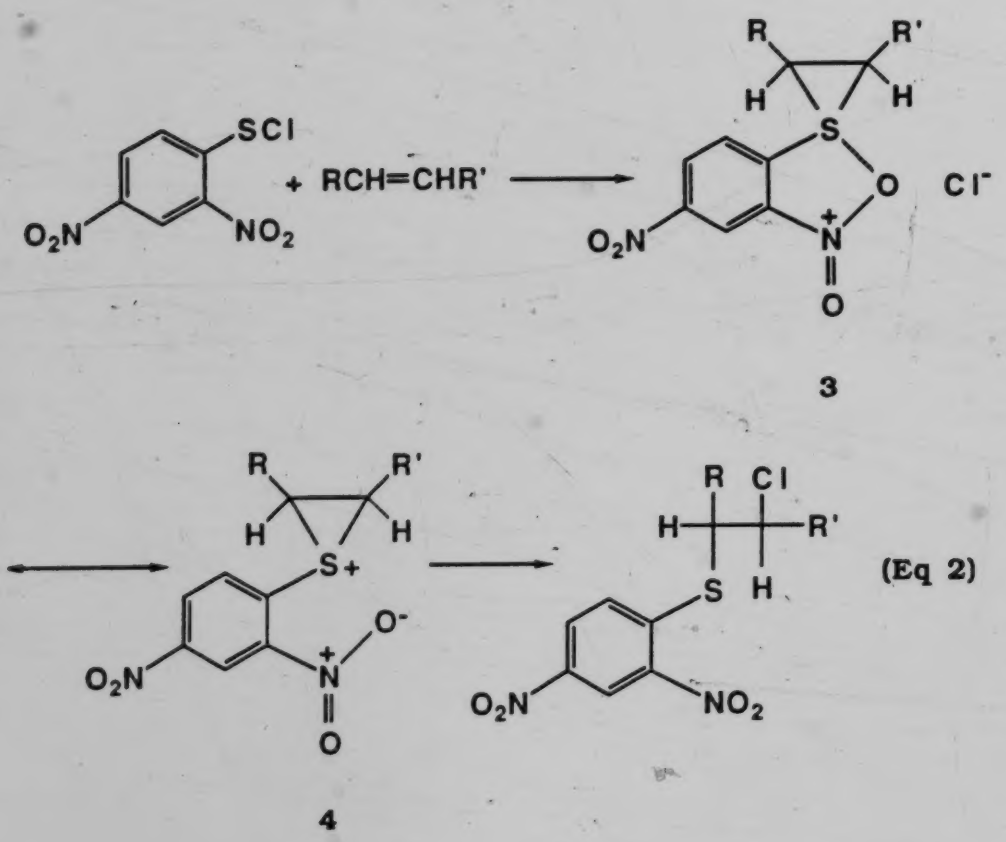


Kharasch[37] contributed much to the study of the mechanism of the addition of sulfenyl chlorides to unsaturated compounds. He was the first to suggest the formation of the now widely accepted cyclic episulfonium intermediate ion **1**, resulting from the reaction of a sulfenyl chloride and an olefin. It was proposed that it is the subsequent opening of the episulfonium ion ring by the chloride anion that then leads to the formation of the β-chloroalkyl sulfide as illustrated in Scheme 1.

Although the general postulate of an episulfonium ion intermediate **1** has been widely accepted, the elucidation of the mechanism of these reactions is continually disputed in literature. Most of Kharasch's studies pertaining to the electrophilic addition mechanism were conducted with 2,4-dinitrobenzenesulfenyl chloride which is considered a convenient model reagent because of its outstanding stability. Whereas the role of the *o*-nitro group in stabilizing the 2,4-dinitrobenzenesulfenium cation was described[38], the bonding interaction between oxygen of a nitro group and sulfur of an episulfonium salt was not postulated, even though bonding capacities seem optimum. The possible role of the *o*-nitro group was best shown in the work of Givens and Kwart[39] on the chlorinolysis of 2-nitrobenzenesulfenyl chlorides in which the complex **2** was postulated as the key intermediate. In view of the affinity of the sulphur atom of complex **1** for nucleophilic centres, it would seem that the existence of the complex **3** in addition to the free episulfonium salt **4** cannot be ruled out (Eq 2).



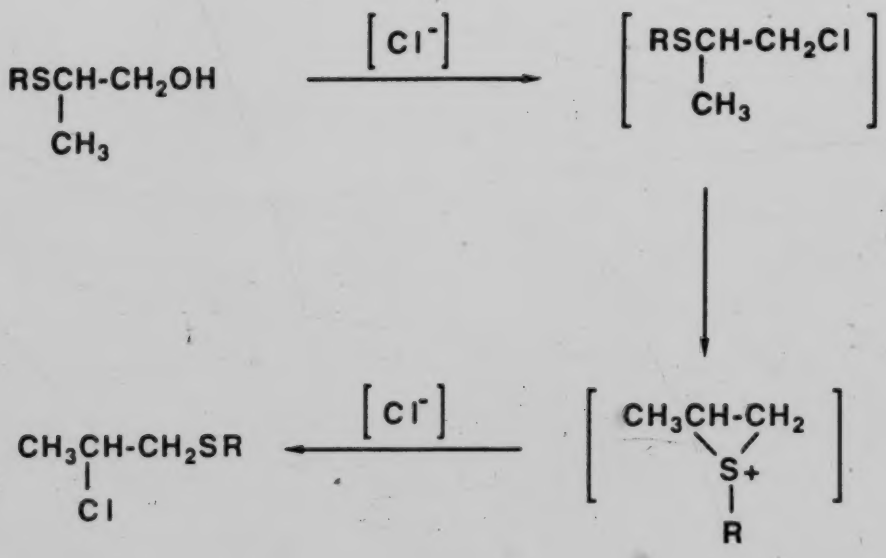
2



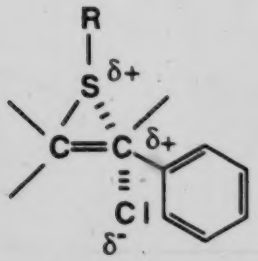
It is generally agreed however, that sulfenyl chloride additions to monoolefins can involve a wide range of subtly different reaction mechanisms. These may range from an episulfonium ion with little charge on the carbon atoms to an intermediate approaching an open carbonium ion in extreme cases. Other important variables like temperature, reaction time and solvent effects can be a major determinant in the reaction course.

As has been illustrated in Scheme 1, sulfenyl chloride additions to unsymmetrically substituted olefins often lead to the formation of regioisomeric products both in accordance with and contrary to the Markovnikov rule[40]. Mueller and Butler[35] in their studies on sulfenyl chloride additions observed a high selectivity for the anti-Markovnikov products with alkyl substituted terminal olefins and, in particular the increase of this selectivity with the size of the alkyl substituent. For example, in going from methyl as in propylene to isopropyl and *t*-butyl as in 3-methylbutene and 3,3-dimethylbutene, higher selectivity for the anti-Markovnikov products was observed. This selectivity ranged from *ca.* 80 to 95% depending on the nature of the sulfenyl chloride being used. This observation was attributed to the influence of steric factors during the episulfonium ring opening by the chloride anion. The isomer distribution ratio remained constant if the product was stored over a small amount of $CaCO_3$ and preferentially at temperatures below O°C. However, in the absence of $CaCO_3$, or a similar base, slow isomerization to the corresponding Markovnikov product took place. They observed that in general, the rearranged isomer ratio contained *ca.* 90% of the Markovnikov product at equilibrium. At ambient temperature equilibration was observed to take place after *ca.* 200 hr. Fuson *et al.*[41] described for the first time the isomerization of β-chloroalkyl sulfides in which the chlorine atom and the methylthio group exchanged places. The authors postulated that the isomerization proceeds via an episulfonium ion as shown in Scheme 2.

Scheme 2



Mueller *et al.*[35] also reported that phenyl substituents on the double bond caused a reversal in the direction of ring opening, favouring Markovnikov adduct orientation. Thus styrene and 1,1-diphenylethylene with methanesulfenyl chloride gave predominantly the Markovnikov adducts with a selectivity of over 90%. The stabilization of the transition state **5** is due to π-bond overlap of the p-orbitals of the electron-deficient α-carbon with the phenyl ring's π-cloud.



5

A number of procedures have been developed for the synthesis of various sulfenyl chlorides. Halogenolysis of corresponding disulfides at low temperature has come to be regarded as the most important and versatile procedure for synthesizing various sulfenyl chlorides. Yields of sulfenyl chlorides prepared in this way are very good as long as the alkyl disulfide residue is not attacked by the chlorine under the reaction conditions. Alkanesulfenyl chlorides, especially those having hydrogen atoms on the α-carbon, are much less stable than the aromatic ones, and are more prone to decomposition. Consequently, the alkanesulfenyl chlorides are not usually isolated, but are prepared as needed at low temperatures. Methanesulfenyl chloride is relatively unstable since it undergoes self-chlorination under the influence of light to give chlorinated alkanesulfenyl chlorides[42,43]. Side reactions of this kind can be suppressed by the use of milder chlorinating agents such as sulfuryl chloride[42] and methylsulfur trichloride[44].

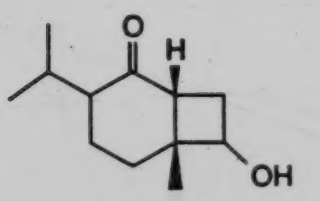
A variety of sulfenyl chlorides can also be prepared by halogenation of thiols[45]. This reaction does not proceed smoothly however; once the desired sulfenyl chloride is formed, it reacts with the unconverted thiol to give the disulfide. The disulfide then gets chlorinated to give the sulfenyl chloride as was described earlier. Side-reactions in the above procedure may be prevented by adding a solution of the thiol in an inert solvent to the chlorinating agent.

The synthesis of sulfenyl chlorides via the halogenation of monosulfides has also been achieved. Zincke[46] has reported the conversion of benzyl thioethers into aromatic sulfenyl chlorides. Chlorination of aryl methyl thioethers leads to different products according to substitution or the position of substituents on the aryl residue. Thus chlorination of 4-methylphenyl methyl thioether gives 4-methylphenyl trichloromethyl thioether. When purely aliphatic thioethers are treated with chlorine, α-chlorinated thioethers are generally obtained in this case. For example, the chlorination of methyl ethyl sulfide gave α-chloroethyl methyl sulfide[47].

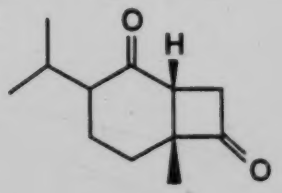
In this part of the thesis, a new and equally facile method which gives rise to β-chloroalkyl sulfides with a high degree of regioselectivity is described.

During the course of synthetic studies on dendrobine, the oxidation of the keto alcohol **6** with oxalyl chloride, dimethyl

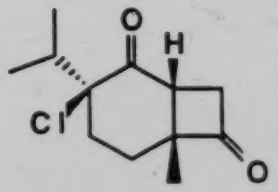
sulfoxide and triethylamine was attempted. Interestingly, instead of the expected diketone **7**, the chlorodiketone **8** was obtained as the major product[14]. This result suggested that the combination of dimethyl sulfoxide and oxalyl chloride also served as a chlorinating agent presumably via the intermediacy of complex **9** [14,13].



6



7



8

$[(CH_3)_2\overset{+}{S}\text{-Cl}]\ Cl^-$

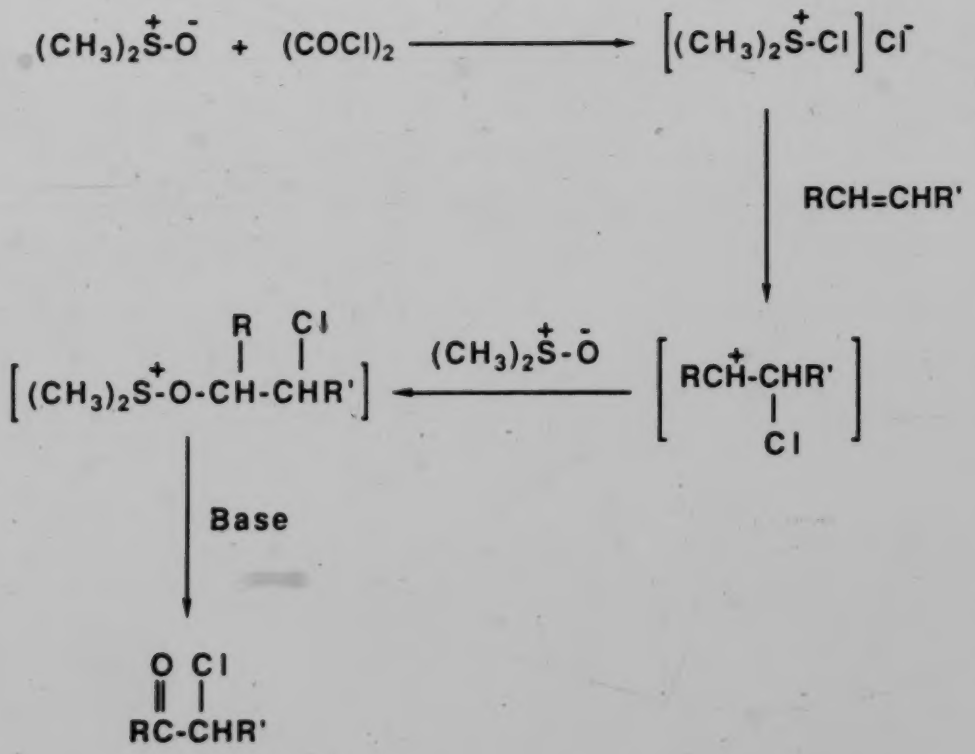
9

On the basis of this observation, it is conceivable that treatment of an olefin with oxalyl chloride and dimethyl sulfoxide in the presence of a base could lead to the formation of the corresponding α-chloroketone via the pathway outlined in Scheme 3. In practice, neither 1-octadecene nor cyclohexene gave the expected products under various reaction conditions. In further studies, the combination of dimethyl sulfoxide and phenyl dichlorophosphate, which has also been shown to be an efficient dimethyl sulfoxide activator[48], was used. Under these conditions, a single compound was produced from 1-octadecene. Unexpectedly,

this compound was characterized as the β-chloroalkyl sulfide **10**. On the basis of this finding, a new method for the formation of β-chloroalkyl sulfide was developed.

$$CH_3(CH_2)_{15}CH(Cl)CH_2SCH_3$$
10

Scheme 3



In an extension of this study, other phosphorus-containing reagents such as phosphorus oxychloride, diethyl chlorophosphate and diphenyl chlorophosphate were also examined, and the results are discussed in this thesis. A simple procedure for the transformation of α- and β-pinenes to chlorides having a limonene skeleton was also developed. This rearrangement reaction is important in that it affords a useful reaction intermediate for further transformation to other useful functionalized monoterpenes. The transformation of α-pinene to carvone in four easy steps is also discussed.

Results and Discussion

As was illustrated in Scheme 3, the transformation of olefins to corresponding α-chloroketones using oxalyl chloride, dimethyl sulfoxide and triethylamine was attempted. Oxalyl chloride (1 eq) in dichloromethane was added to dimethyl sulfoxide (2 eq) in dichloromethane at -60°C. 1-Octadecene (1 eq) was then added and temperature allowed to rise to -20°C. Triethylamine (5 eq) was then added slowly and after stirring for 10 min, the reaction mixture was allowed to warm up to room temperature. After stirring for 3 hr, only the starting material (70%) was recovered. By mixing the reagents at -20°C rather than -60°C, followed by warming to room temperature, only starting material was recovered. Reaction conditions were varied further by adjusting the amount of reagents: i.e. increasing the amount of oxalyl chloride from 1 eq to 3 eq and likewise increasing the amount of dimethyl sulfoxide from 2 eq to 6 eq, again met with the same results. Cyclohexene was subsequently used in the place of 1-octadecene as the substrate for this transformation, however similar results were obtained.

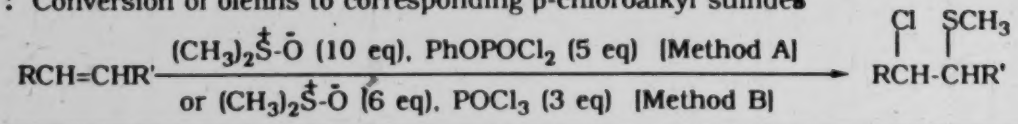
In further studies, the combination of dimethyl sulfoxide and phenyl dichlorophosphate, which has also been shown to be an efficient dimethyl sulfoxide activator[48], was used. With 1-octadecene (Entry 1) as the substrate, a single compound was

produced. Unexpectedly, the product was not the α-chloroketone but rather the β-chloroalkyl sulfide compound **10**. In the ^1H nmr spectrum this compound exhibited a singlet at δ2.16 due to a methyl group next to a sulfur atom, a multiplet at δ4.02 due to a proton on the carbon bearing a chlorine atom. A pair of doublets of doublets at δ2.91 (J=6, J'=13.5 Hz) and 2.82 (J=7.5, J'=13.5 Hz) were assigned to the methylene protons adjacent to the sulfur atom. The mass spectrum showed the molecular ion peaks at 334.2465 and 336.2441 consistent with the chemical formula $C_{19}H_{39}SCl$.

On the basis of this finding, a new method for the formation of β-chloroalkyl sulfides was developed. The general procedure which was successfully applied to all the olefins examined in this study is described below. To a solution of phenyl dichlorophosphate (5 eq) in dry methylene chloride at -20°C under an argon atmosphere, is added with stirring, dimethyl sulfoxide (10 eq). After stirring for 5 min, the olefin is introduced. The mixture is then stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. The results obtained for the various olefins that were examined in this study are summarized in Table 1.

It is evident from Table 1 that, with unsymmetrically substituted terminal double bonds, the addition proceeded in a completely regioselective manner with the methylthio group being added to the carbon bearing the greater number of hydrogen atoms (Entries 1, 3 and 4). This is in complete contrast to what was observed when various sulfenyl chlorides were added to various

Table 1 : Conversion of olefins to corresponding β-chloroalkyl sulfides



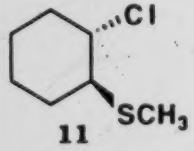
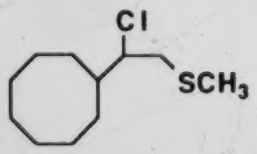
Entry	Substrate	Time(min)	Temp(°C)	Product	% Yield (Method)	
1	$CH_3(CH_2)_{15}CH=CH_2$	70	-20 → 20	$CH_3(CH_2)_{15}CH(Cl)CH_2SCH_3$ **10**	79 (A)	76 (B)
2		60	-20 → 20	 **11**	80 (A)	52 (B)
3	$CH_3(CH_2)_{11}CH=CH_2$	70	-20 → 20	$CH_3(CH_2)_{11}CH(Cl)CH_2SCH_3$	81 (A)	78 (B)
4		45	-20 → 20		83 (A)	81 (B)

Table 1 : (contd.)

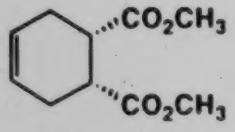
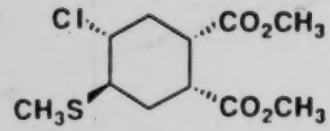
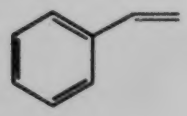
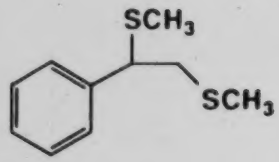
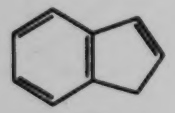
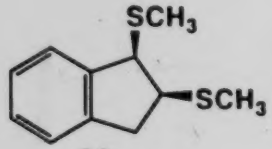
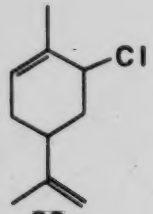
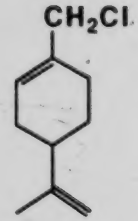
Entry	Substrate	Time(min)	Temp(°C)	Product	% Yield (Method)
5	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2CH_3$ **12**	75	-20 → 20	$CH_3(CH_2)_7CH(Cl)CH(SCH_3)(CH_2)_7CO_2CH_3$ **13** + $CH_3(CH_2)_7CH(SCH_3)CH(Cl)(CH_2)_7CO_2CH_3$ **14** (~ 1:1)	81 (A) 79 (B)
6	 **15**	70	-20 → 20	 **16**	80 (A) 82 (B)
7	 **17**	60	-20 → 20	 **18**	83 (A) 81 (B)

Table 1: (contd.)

Entry	Substrate	Time(min)	Temp(°C)	Product	% Yield (Method)
8	 29	60	-20→20	 20	82 (A) 81 (B)
9	22	25	-20→20	 23	97 (A) 100 (B)
10	27	25	-20→20	 28	95 (A) 100 (B)

terminal double bonds in terms of both the orientation and degree of selectivity[32]. The stereoselectivity on the other hand was found to be the same as that observed for sulfenyl chlorides with exclusive *trans*-addition[32,35]. Thus, the treatment of cyclohexene (Entry 2) with phenyl dichlorophosphate and dimethyl sulfoxide gave the adduct **11** as the sole product in 80% yield. From the ^1H nmr spectrum, this adduct shows a pair of doublets of doublets of doublets at δ4.05 (J=4, J'=8, J"=8 Hz) due to the proton on the carbon bearing the chlorine atom and at δ2.75 (J=4, J'=8, J"=8 Hz) for the proton on the carbon with the methylthio group. The structure was further confirmed by the mass spectrum showing the required molecular ion peaks at 164.0427 and 166.0398 consistent with $C_7H_{13}SCl$.

This procedure was also found to be applicable to compounds containing other functionalities. For example, the methyl ester **12** (Enty 5) was readily transformed to the corresponding isomeric adducts **13** and **14** in a 1:1 ratio and a total yield of 81%. The reaction of the diester **15** (Entry 6) under the same reaction conditions gave the adduct **16** as the sole product in 80% yield. This compound exhibited an absorption band at 1736 cm^{-1} for the ester carbonyls. The mass spectrum showed the molecular ion peaks at 280.0522 and 282.0493 due to the chemical formula $C_{11}H_{17}O_4SCl$.

The reaction of styrene (**17**) with phenyl dichlorophosphate and dimethyl sulfoxide produced an unexpected product which was

characterized as the adduct **18** in 83% yield. The ^1H nmr spectrum showed two singlets for the two methyl groups adjacent to sulfur atoms at δ1.95 and 2.02. A pair of doublets of doublets at δ2.95 and 3.04 were assigned for the only methylene protons in the structure. Another doublet of doublets due to the benzylic proton appeared at δ3.98. The proposed structure was further confirmed from the mass spectrum which showed the molecular ion peak at 198.0544 which is consistent with the chemical formula $C_{10}H_{14}S_2$. This was an unusual result because the expected chlorine atom at the benzylic carbon may have been displaced by a methylthio group to give the adduct **18**. To confirm the results obtained for styrene (**17**), indene (**19**) was treated under the same reaction conditions. As was observed for styrene (**17**), the treatment of indene (**19**) with dimethyl sulfoxide and phenyl dichlorophosphate led to the formation of the adduct **20** as the only detectable product in excellent yield. The mass spectrum showed the molecular ion peak at 210.0538 due to the chemical formular $C_{11}H_{14}S_2$. The ^1H nmr spectrum showed a pair of singlets at δ2.05 and 2.16 for the two methyl groups adjacent to sulfur atoms. A doublet due to the methine proton on the benzylic carbon was observed at δ4.20.

The mechanistic pathway leading to the formation of the adducts **18** and **20** from styrene (**17**) and indene (**19**) is not clearly understood at this stage. It is highly likely however, that dimethyl sulfide could serve as a source of the methylthio moiety on the benzylic carbon. A likely source of the dimethyl sulfide is from the

disproportionation of the dimethyl sulfenyl chloride complex **9** which could be produced from the initial complex **21**.

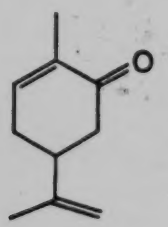
$$[(CH_3)_2\overset{+}{S}OPO(R)Cl]\ Cl^-$$

21

An interesting result was obtained when α-pinene (**22**) was treated with phenyl dichlorophosphate and dimethyl sulfoxide. Instead of the expected β-chloroalkyl sulfide, the rearrangement product, the chloride **23** was the only product obtained in almost quantitative yield. The structure of this compound was readily deduced from the spectral data. The mass spectrum showed molecular ion peaks at 170.0860 and 172.0831 in agreement with the required molecular formula of $C_{10}H_{15}Cl$. The ^1H nmr spectrum showed three vinylic protons as multiplets centred at δ5.62, 4.76 and 4.70. The methine proton adjacent to the chlorine atom appeared at δ4.52 also as a multiplet. Two broad singlets were observed for the vinylic methyl groups at δ1.80 and 1.74.

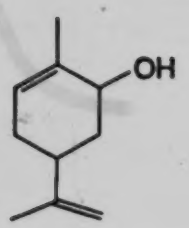
The conversion of α-pinene (**22**) to the chloride **23** is an important transformation in that it affords the limonene skeleton which in principle can be used as an intermediate for various other monoterpene transformations. Carvone (**24**) a naturally occuring monoterpene which is a very important ingredient in flavouring liqueurs, perfumes and soaps[49] was readily synthesized from the

chloride **23** in four simple operations. Because of its commercial importance, an economical procedure for producing carvone (**24**) is desirable[50,51]. A number of the existing syntheses for carvone (**24**) are low yielding[52,53], operationally complex and some of them use highly toxic reagents[54], making them undesirable as commercial processes.

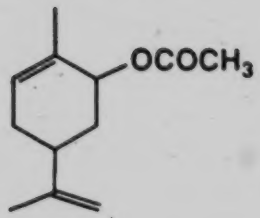


24

The transformation of the chloride **23** to the target compound **24** could in principle, be carried out by converting the chloride **23** directly to the corresponding alcohol **25** followed by oxidation. In practice however, the direct transformation of compound **23** to the alcohol **25** proved to be difficult. Treatment of the chloride **23** with silver oxide, potassium carbonate, or sodium hydroxide under a variety of reaction conditions gave only poor yields (<30%) of the desired alcohol **25**.



25



26

As a consequence of the above observations, the transformation of the chloride **23** to the alcohol **25** was carried out indirectly in two synthetic operations. The chloride **23** was first subjected to treatment with silver acetate in refluxing glacial acetic acid to afford the acetate **26** in 86% yield. The ir spectrum showed the characteristic ester absorption band at 1738 cm^{-1}. The mass spectrum showed a molecular ion peak at 194.1312 for the required chemical formula of $C_{12}H_{18}O_2$. The ^1H nmr spectrum displayed a sharp methyl singlet at δ2.12 for the newly introduced acetoxy group. The vinylic methyl groups appeared as multiplets centred at *ca.* δ1.70 and 1.60, while the two methylidene protons were observed at δ4.74 also as a multiplet. The presence of two sets of signals in the δ5 to 6 region in a 5:3 ratio indicates the presence of two stereoisomers. The major set of signals appeared at δ5.28 and 5.76 for the methine proton neighbouring the acetoxy group and the proton attached to trisubstituted double bond respectively. In the minor isomer, these signals appeared at δ5.46 and 5.61 respectively.

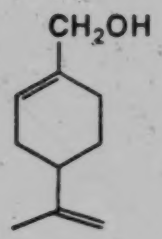
The acetate **26** was then hydrolyzed by refluxing with aqueous potassium carbonate in methanol. The desired alcohol **25** was obtained in quantitative yield. The spectral data of the alcohol **25** was found to be in agreement with that of an authentic sample.

The alcohol **25** was then oxidized with phenyl dichlorophosphate, dimethyl sulfoxide and triethylamine to afford carvone (**24**) in 81% yield. This product showed characteristic conjugated enone absorption bands in the ir spectrum at 1673 and 1644 cm^{-1}. In the ^1H nmr spectrum, the vinylic proton of the enone system appeared at δ6.78 as a multiplet and the other vinylic protons were found at δ4.82 as a triplet (J=7.5 Hz) and at δ4.77 as a broad singlet. Two vinylic methyl groups were also observed; one at δ1.80 as a narrowly split multiplet and the other at δ1.77 as a broad singlet. The mass spectrum showed the molecular ion peak at 150.1042 due to $C_{10}H_{14}O$. Carvone (**24**) was obtained in an overall yield of 70% from α-pinene in four easy transformations.

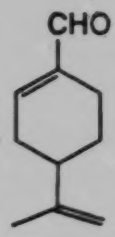
When β-pinene (**27**) was treated with phenyl dichlorophosphate and dimethyl sulfoxide, a similar rearrangement as was observed for α-pinene (**22**) took place to give the chloride **28** in almost quantitative yield. The ^1H nmr spectrum of the chloride **28** showed a vinylic methyl group at δ1.75 as a broad singlet. The methylene group adjacent to the chlorine atom appeared at δ4.02 as a singlet. The two methylidene protons were observed as a broad singlet at δ4.74 while the vinylic proton appeared as a broad singlet at δ5.85. The molecular ion peaks in the mass spectrum were

observed at 170.0863 and 172.0838 for the required chemical formula of $C_{10}H_{15}Cl$.

The chloride **28** obtained from β-pinene also has the basic limonene skeleton which can be used in further transformations to afford other functionalized monoterpenes. In principle, perillyl alcohol (**29**) can be prepared readily by substitution of the chlorine atom with a hydroxy group. The oxidation of the perillyl alcohol (**29**) leads to perillaldehyde (**30**).



29

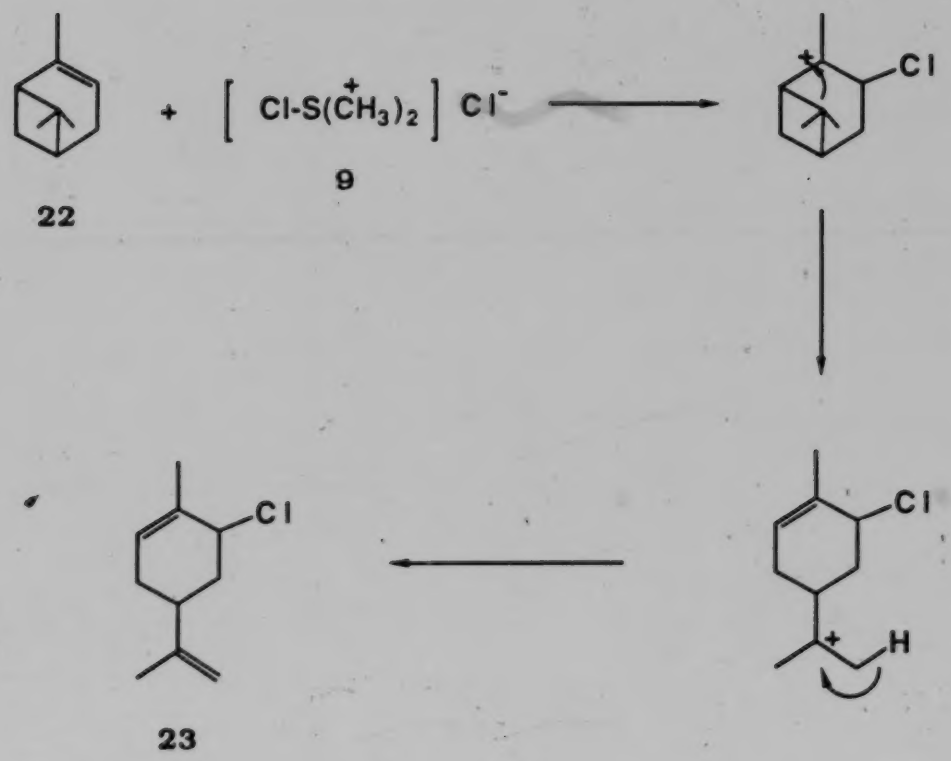


30

A probable mechanistic pathway for the rearrangement reaction of α-pinene **22** to the chloride **23** is illustrated in Scheme 4. The reaction of dimethyl sulfoxide and phenyl dichlorophosphate presumably would lead to the formation of the intermediate complex **21** from which the dimethylsulfenyl chloride complex **9** can be formed. As was shown earlier, it is the complex **9** which could serve as the source for positive chlorine[13,14]. The subsequent reaction of the complex **9** with the highly strained

pinene system affords the observed product via the proposed rearrangement.

Scheme 4



22 9 23

During the course of this study, other phosphorus-containing reagents were examined such as diethyl chlorophosphate, diphenyl chlorophosphate and phosphorus oxychloride. Of these reagents, phosphorus oxychloride emerged also as an efficient dimethyl sulfoxide activator in the transformation of olefins to β-chloroalkyl sulfides. Although phosphorus oxychloride has not been found to be

an efficient dimethyl sulfoxide activator in the oxidation of alcohols to their corresponding carbonyls, it does however react readily with dimethyl sulfoxide at low temperatures to form the complex **21**.

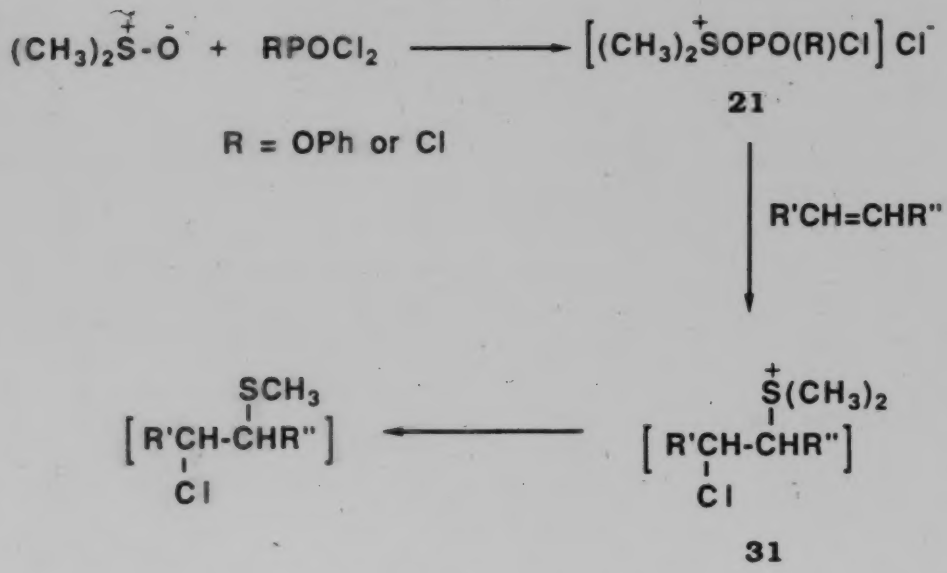
The general procedure which was applied to all the olefins examined for phosphorus oxychloride is described below. Phosphorus oxychloride (3 eq) was added to a solution of dimethyl sulfoxide (6 eq) in dichloromethane at -20°C. After stirring for 5 min, the olefin (1 eq) was introduced. The reaction mixture was stirred for 5 min at -20°C and then allowed to warm up slowly to room temperature. The results obtained for this procedure using phosphorus oxychloride are also summarized in Table 1.

It is evident from the Table 1 that the yields of products obtained using phosphorus oxychloride compare favourably to those obtained for phenyl dichlorophosphate with very few exceptions. A notable exception was observed for cyclohexene. Only a 52% yield of the product **11** was obtained with phosphorus oxychloride compared to the 80% yield obtained when phenyl dichlorophosphate was used.

Treatment of styrene (**17**) and indene (**19**) with phosphorus oxychloride and dimethyl sulfoxide gave the disulphides **20** and **21** respectively in excellent yields. Both α-pinene (**22**) and β-pinene (**27**) were readily converted to the chloro compounds **23** and **28** respectively in quantitative yields, presumably via the proposed rearrangement in Scheme 4.

The formation of β-chloroalkyl sulfides using both phosphorus oxychloride and phenyl dichlorophosphate can be rationalized by invoking the initial formation of the complex **21**, arising from the reaction of dimethyl sulfoxide and the phosphorus reagents which serve as electrophiles. As outlined in Scheme 5, the complex **21** in the presence of an olefin would presumably lead to the formation of the intermediate **31** and subsequently to the corresponding β-chloroalkyl sulfide product.

Scheme 5



Experimental

General

For general remarks see Chapter 1 of this thesis.

Materials

Argon and solvents used were purified as described in Chapter 1 of this thesis.

2-Chloro-1-(methylthio)octadecane (10)

$$CH_3(CH_2)_{15}CH(Cl)CH_2SCH_3$$
10

(a) Using $PhOPOCl_2$ / Dimethyl sulfoxide

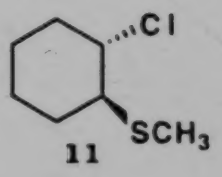
To a solution of dimethyl sulfoxide (0.7 mL, 10 mmol) in dry dichloromethane (5 mL) at -20°C under an argon atmosphere was added phenyl dichlorophosphate (0.75 mL, 5 mmol). After 5 min, 1-octadecene (0.35 mL, 1 mmol) was introduced. The mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After 1 hr, water was added, the organic layer separated and the aqueous layer extracted with dichloromethane (3x20 mL). The combined organic solutions were washed with saturated sodium chloride solution, dried with magnesium sulfate and filtered. Concentration followed by flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum

ether gave the β-chloroalkyl sulfide **10** (263 mg, 79% yield): ir 2929, 2853 cm^{-1} (CH_3, CH_2); ^1H nmr δ0.88 (t, 3H, J=7 Hz, $-CH_2CH_3$), 1.25 (br, s, 30H, $-(CH_2)_{15}-$), 2.16 (s, 3H, CH_3S-), 2.82 (dd, 1H, J=6.5, J"=13.5 Hz, $-CHHSCH_3$), 2.92 (dd, 1H, J=7.5, J"=13.5 Hz, $-CHHSCH_3$), and 4.02 (m, 1H, $-CH_2CH(Cl)CH_2-$); ms M^+ 334.2465 and 336.2441 (cald. for $C_{19}H_{39}SCl$: 334.2461 and 336.2432).

(b) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.42 mL, 6 mmol) was added to a solution of phosphorus oxychloride (0.28 mL, 3 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, 1-octadecene (0.35, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether gave the adduct **10** (253 mg, 76% yield). The ir, ^1H nmr and mass spectra were identical to those reported previously (*vide supra*).

1-Chloro-2-(methylthio)cyclohexane (11)



11

(a) Using $PhOPOCl_2$ / Dimethyl sulfoxide

To a solution of phenyl dichlorophosphate (1.5 mL, 10 mmol) in freshly distilled methylene chloride (5 mL) at -20°C under argon atmosphere was added dimethyl sulfoxide (1.4 mL, 20 mmol). After stirring for 5 min, cyclohexene (165 mg, 2 mmol) was added. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After 50 min, water was added, the organic layer separated and the aqueous layer extracted with methylene chloride (3x25 mL). The combined organic solutions were washed with saturated sodium chloride solution, dried with magnesium sulfate and filtered. Concentration followed by flash chromatography of the residue on silica gel, eluting with 15% diethyl ether in petroleum ether afforded the adduct **11** (262 mg, 80% yield): ^{1}H nmr δ2.18 (s, 3H, CH_3S-), 2.75 (ddd, 1H, J=4, J'=8, J"=8 Hz, -CH(SCH_3)-) and 4.04 (ddd, 1H, J=4, J'=8, J"=8 Hz, -CH(Cl)-); ms M^+ 164.0427 and 166.0398 (calcd. for $C_7H_{13}SCl$: 164.0426 and 166.0397).

(b) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.42 mL, 6 mmol) was added to a solution of phosphorus oxychloride (0.28 mL, 3 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, cyclohexene (82 mg, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave the adduct **11** (85 mg, 52% yield). The ir, ^1H nmr and mass spectra were identical to those reported previously (*vide supra*).

2-Chloro-1-(methylthio)tetradecane

$$CH_3(CH_2)_{11}CH(Cl)CH_2SCH_3$$

(a) Using $PhOPOCl_2$ / Dimethyl sulfoxide

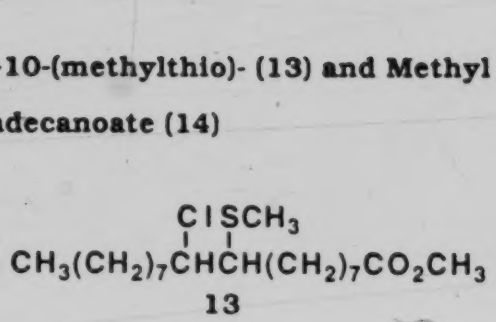
A solution of dimethyl sulfoxide (0.7 mL, 10 mmol) in dry dichloromethane (5 mL) was added to phenyl dichlorophosphate (0.75 mL, 5 mmol) at -20°C under an argon atmosphere. After stirring for 5 min at -20°C, 1-tetradecene (196 mg, 1 mmol) was added. The reaction mixture was stirred at -20°C for 5 min and then allowed to slowly warm up to room temperature. After 1 hr,

water was added, the organic layer separated and the aqueous layer extracted with dichloromethane (3x25 mL). The combined organic solutions were dried with anhydrous magnesium sulfate and filtered. Concentration followed by flash column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether afforded 2-chloro-1-(methylthio)tetradecane (225 mg, 81% yield): ir 2953, 2853 cm^{-1} (CH_3, CH_2); ^1H nmr δ0.88 (t, 3H, J=7 Hz, CH_3CH_2-), 1.28 (br, s, 22H, -$(CH_2)_{11}$-), 2.16 (s, 3H, CH_3S-), 2.82 (dd, 1H, J=6, J'=13.5 Hz, CH_3SCHH-), 2.93 (dd, 1H, J=8, J'=13.5 Hz, CH_3SCHH-) and 4.04 (m, 1H, -$CH_2CH(Cl)CH_2$-); ms M^+ 278.1833 and 280.1810(calcd. for $C_{15}H_{31}SCl$: 278.1835 and 280.1804).

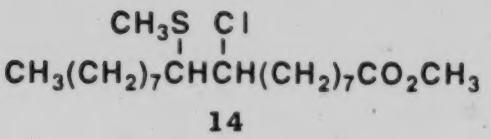
(*b*) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.42 mL, 6 mmol) was added to a solution of phosphorus oxychloride (0.28 mL, 3 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, 1-tetradecene (196 mg, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether gave 2-chloro-1-(methylthio)tetradecane (217 mg, 78% yield). The ir, ^1H nmr and mass spectra were identical to those reported previously (*vide supra*).

Methyl 9-Chloro-10-(methylthio)- (13) and Methyl 10-Chloro-9-(methylthio)nonadecanoate (14)



13



14

(a) Using $PhOPOCl_2$ / Dimethyl sulfoxide

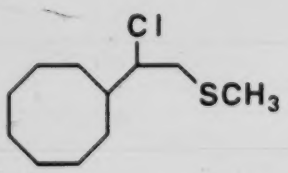
Dimethyl sulfoxide (0.7 mL, 10 mmol) was added to a solution of phenyl dichlorophosphate (0.75 mL, 5 mmol) in dry dichloromethane (5 mL) at -20°C under an argon atmosphere. After stirring at -20°C for 5 min, the ester compound **12** (296 mg, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After 65 min, water was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The combined organic solutions were dried with magnesium sulfate, filtered and concentrated. Flash column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave a mixture of adducts **13** and **14** (306 mg, 81% yield): ^{1}H nmr δ3.68 (s, 3H, $-CO_2CH_3$), 2.15 (s, 3H, $-SCH_3$), 2.30 (t, 2H, J=7 Hz, $-CH_2CO-$), 2.74 (br, m, 1H, $-CH(SCH_3)-$) and

4.10 (br. m. -C**H**(Cl)-); ms M^+ 378.2352 and 380.2318 (calcd. for $C_{20}H_{39}O_2SCl$: 378.2359 and 380.2330)

(*b*) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.42 mL, 6 mmol) was added to a solution of phosphorus oxychloride (0.28 mL, 3 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, the ester compound **12** (296 mg, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether gave a mixture of adducts **13** and **14** (298 mg, 79% yield). The ir, ^1H nmr and mass spectra were identical to those reported previously (*vide supra*).

(1-Chloro-3-thiabutyl)cyclooctane



(*a*) Using $PhOPOCl_2$ / Dimethyl sulfoxide

Phenyl dichlorophosphate (1.5 mL, 10 mmol) was added to dimethyl sulfoxide (1.4 mL, 20 mmol) in dry methylene chloride (5

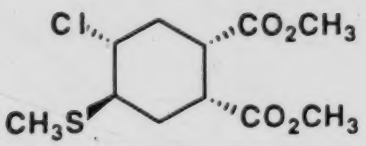
mL) at -20°C under an argon atmosphere. Vinylcyclooctane (276 mg, 2 mmol).) was then introduced after stirring for 5 min. The reaction mixture was stirred at -20°C for another 5 min and then allowed to slowly warm up to room temperature. After 35 min, water was added and the aqueous layer separated. The aqueous layer was then extracted with dichloromethane (3x25 mL). The combined organic solutions were dried with magnesium sulfate, filtered and concentrated. Purification of the resulting residue on a silica gel column, eluting with 15% diethyl ether in petroleum ether afforded the (1-chloro-3-thiabutyl)cyclooctane (365 mg, 83% yield): ir 2921, 2852 cm^{-1} (CH_3, CH_2); ^1H nmr δ2.18 (s, 3H, CH_3S-), 2.84 (dd, 1H, J=7.5, J'=14 Hz, CH_3SCHH-), 2.90 (dd, 1H, J=8.5, J'=14 Hz, CH_3SCHH-) and 4.04 (dt, 1H, J=3 Hz, J'=7.5 Hz, -$CH(Cl)CH_2$-); ms M^+ 220.1012 and 222.0973 (calcd. for $C_{11}H_{21}SCl$: 220.1052 and 222.1023).

(*b*) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.42 mL, 6 mmol) was added to a solution of phosphorus oxychloride (0.28 mL, 3 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, vinylcyclooctane (138 mg, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 15%

diethyl ether in petroleum ether gave (1-chloro-3-thiabutyl)cyclooctane (179 mg, 81% yield). The ir, ^{1}H nmr and mass spectra were identical to those reported previously (*vide supra*).

(1R*, 2S*, 4R*, 5R*)-1,2-Dicarbomethoxy-4-chloro-5-(methylthio)cyclohexane (16)



16

(a) Using $PhOPOCl_2$ / Dimethyl sulfoxide

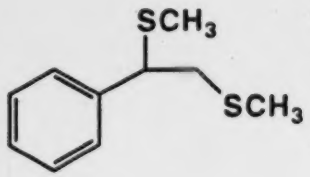
To a solution of phenyl dichlorophosphate (1.5 mL, 10 mmol) at -20°C in dry dichloromethane, was added dimethyl sulfoxide (1.4 mL, 20 mmol). After stirring for 5 min, the diester **15** (396 mg, 2 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to slowly warm up to room temperature. After 1 hr, water was added, the organic layer separated and the aqueous layer extracted with dichloromethane (3x25 mL). The combined organic solutions were dried with magnesium sulfate, filtered and concentrated. The resulting residue was purified on a silica gel column, eluting with 15% ethyl acetate in petroleum ether to give the adduct **16** (448 mg, 80% yield): ir 1736 cm^{-1} (ester C=O); ^{1}H nmr δ2.20 (s, 3H, CH_3S-), 3.69 and 3.71 (s, total 6H, 2x -CO_2CH_3), 2.80 and 2.87 (br, m, total 2H, 2x -CH-CO_2CH_3), 2.60

(ddd, 1H, J=4, J'=4, J"=14.5 Hz, -CH(Cl)C**H**H- (equatorial)), 2.38 (ddd, 1H, J=9, J'=9, J"=14.5 Hz, -CH(Cl)CH**H**- (axial)), 2.70 (ddd, 1H, J=4, J'=6, J"=15 Hz, -CH(SCH_3)C**H**H- (equatorial)), 1.85 (ddd, 1H, J=4, J'=9, J"=15 Hz, -CH(SCH_3)CH**H**- (axial)), 3.13 (br, m, 1H, -C**H**-SCH_3) and 3.96 (br, m, 1H, -C**H**-Cl); ms M^+ 280.0522 and 282.0493 (calcd. for $C_{11}H_{17}O_4SCl$: 280.0536 and 282.0507). From nOe experiments, an enhancement of 4.3% was observed on signal at δ2.87 when the proton at δ3.96 was irradiated.

(*b*) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.42 mL, 6 mmol) was added to a solution of phosphorus oxychloride (0.28 mL, 3 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, the diester **15** (198 mg, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave the adduct **16** (230 mg, 82% yield). The ir, ^1H nmr and mass spectra were identical to those reported previously (*vide supra*).

(1,2-Dimethylthioethyl)benzene (18)



18

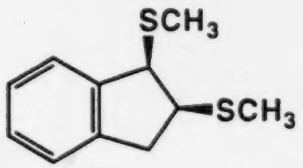
(*a*) Using $PhOPOCl_2$ / Dimethyl sulfoxide

A solution of phenyl dichlorophosphate (1.5 mL, 10 mmol) in freshly distilled dichloromethane (5 mL) was added to dimethyl sulfoxide (1.4 mL, 20 mmol) in dry dichloromethane (5 mL) at -20°C. After stirring for 6 min, styrene (**17**) (160 mg, 2 mmol) was added. The reaction mixture was stirred for 5 min at -20°C and then slowly warm up to room temperature. After 50 min, water was added, the organic layer separated and the aqueous layer extracted with dichloromethane (3x25 mL). The combined organic solutions were dried with magnesium sulfate, filtered and concentrated. The resulting residue was subjected to flash chromatography on silica gel, eluting with 15% ethyl acetate in petroleum ether to afford the adduct **18** (329 mg, 83%): ir ; ^{1}H nmr δ2.02, 1.95 (both s, 3H each, 2x CH_3S-), 3.04 (dd, 1H, J=6, J'=13.5 Hz, CH_3SCHH-), 2.95 (dd, 1H, J=9, J'=13.5 Hz, CH_3SCHH-), 3.89 (dd, 1H, J=7, J'=7.5 Hz, -$CH_2CH(SCH_3)$-) and 7.35 (m, 5H, aromatic protons); ms M^+ 198.0544 (calcd. for $C_{10}H_{14}S_2$: 198.0537).

(*b*) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.42 mL, 6 mmol) was added to a solution of phosphorus oxychloride (0.28 mL, 3 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, styrene (**17**) (80 mg, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave the adduct **18** (161 mg, 81% yield). The ir, ^1H nmr and mass spectra were identical to those reported previously (*vide supra*).

1,2-(Dimethylthio)indan (20)



20

(*a*) Using $PhOPOCl_2$ / Dimethyl sulfoxide

To a solution of dimethyl sulfoxide (0.7 mL, 10 mmol) in dry dichloromethane (5 mL) at -20°C was added phenyl dichlorophosphate (0.75 mL, 5 mmol). After stirring for 5 min, indene (**19**) (116 mg, 1 mmol) was introduced. The reaction

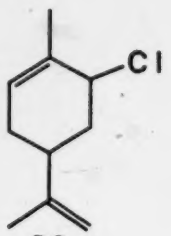
mixture was stirred for another 5 min at -20°C and then allowed to slowly warm up to room temperature. After 50 min, water was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The combined organic solutions were washed with saturated sodium chloride, dried with magnesium sulfate, filtered and concentrated. Flash column chromatography of the resulting residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave the adduct **20** (172 mg, 82%): ir 3018 cm^{-1} (=C-H); ^1H nmr δ7.25 (m, 4H, aromatic protons), 4.20 (d, 1H, J=4 Hz, -C**H**(SCH_3)-), 3.50 (ddd, 1H, J=7.5, J'=7.5, J"=4.5 Hz, -C**H**(SCH_3)CH_2-), 3.48 (dd, 1H, J=7.5, J'=19.5 Hz, -CH(SCH_3)C**H**H-) 2.92 (dd, 1H, J=7.5, J'=19.5 Hz, -CH(SCH_3)CH**H**-), 2.18 and 2.06 (s, total 6H, 2x -SC**H**$_3$); ms M^+ 210.0538 (calcd. for $C_{11}H_{14}S_2$: 210.0537). From nOe experiments, an enhancement of 3.7% was observed for the signal at δ3.50 when the proton at δ4.20 was irradiated.

(*b*) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.42 mL, 6 mmol) was added to a solution of phosphorus oxychloride (0.28 mL, 3 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, indene (**19**) (116 mg, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash

chromatography of the residue on silica gel, eluting with 15% ethyl acetate in petroleum ether gave the adduct **20** (170 mg, 81% yield). The ir, ^{1}H nmr and mass spectra were identical to those reported previously (*vide supra*).

6-Chloro-4-isopropenyl-1-methylcyclohexene (23)



23

(*a*) Using $PhOPOCl_2$ / Dimethyl sulfoxide

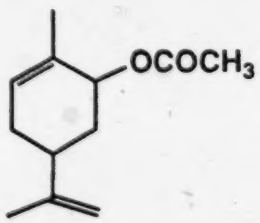
To a solution of α-pinene (**22**) (1.59 mL, 10 mmol) in dry dichloromethane (10 mL) at -20°C under an atmosphere of argon, were sequentially added dimethyl sulfoxide (2.84 mL, 40 mmol) and phenyl dichlorophosphate (3.0 mL, 20 mmol). The resulting solution was stirred for 5 min at -20°C and then allowed to slowly warm up to room temperature. After 20 min, water was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x30 mL) and the combined organic solutions dried over magnesium sulfate, filtered and concentrated. The resulting residue was subjected to flash column chromatography, eluting with 5% diethyl ether in petroleum ether to give the chloride **23** (1.67 g, 97% yield): ir 3021 cm^{-1} (=C-H); ^{1}H nmr δ5.62 (m, 1H, -C**H**=), 4.76 (m, 1H, =C**H**H), 4.70 (m, 1H, =CH**H**), 4.52 (m,

1H, -CH(Cl)-), 1.86 and 1.90 (br. s, total 6H, 2x CH_3-); ms M^+ 170.0860 and 172.0931 (calcd. for $C_{10}H_{15}Cl$: 170.0864 and 172..0834).

(b) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.14 mL, 2 mmol) was added to a solution of phosphorus oxychloride (0.10 mL, 1 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, α-pinene (**22**) (0.16 mL, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% diethyl ether in petroleum ether gave the chloride **23** (171 mg, 100% yield). The ir, ^1H nmr and mass spectra were identical to those reported previously (*vide supra*).

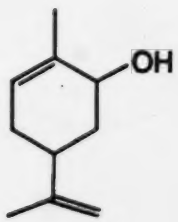
6-Acetoxy-4-isopropenyl-1-methylcyclohexene (26)



26

To a solution of the chloride **23** (1.72g, 10 mmol) in glacial acetic acid (20 mL) was added silver acetate (2g, 12 mmol). The reaction mixture was heated at reflux under an argon atmosphere with stirring for 1 hr. After cooling to room temperature, the mixture was filtered and the residue washed thoroughly with dichloromethane. The filtrate was washed with saturated aqueous sodium carbonate and with water, dried over magnesium sulfate, filtered and concentrated. Flash column chromatography of the resulting residue on silica gel, eluting with 10% ethyl acetate in petroleum ether afforded the acetate **26** (1.67g, 86% yield): ir 1738 cm^{-1} (ester carbonyl); The ^1H nmr spectrum exhibited two sets of signals. The following ^1H nmr data were attributed to the major isomer: δ5.76 (m, 1H, =C**H**-), 5.28 (m, 1H, CH_3CO_2C**H**-), 4.74 (m, 2H, =CH_2), 2.12 (s, 3H, CH_3CO-), 1.70 and 1.60 (m, total 6H, 2x CH_3-). The following data were attributed to the minor isomer: δ5.61 (m, 1H, =C**H**-), 5.46 (m, 1H, CH_3CO_2C**H**-), 4.74 (m, 2H, =CH_2), 2.12 (s, 3H, CH_3CO-), 1.70 and 1.60 (m, total 6H, 2x CH_3-); ms M^+ 194.1312 (calcd. for $C_{12}H_{18}O_2$: 194.1307).

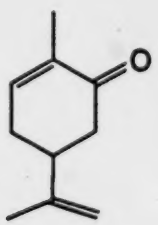
6-Hydroxy-4-isopropenyl-1-methylcyclohexene (25)



25

A solution of the acetate **26** (1.67g, 8.6 mmol) and potassium carbonate (2.37g, 17.2 mmol) in water (10 mL) and methanol (30 mL) was heated at reflux under an argon atmosphere for 1.25 hr. The resulting mixture was concentrated to a volume of ca. 10 mL and cold water added. The solution was then extracted with chloroform (3x30 mL) and the combined extracts dried over magnesium sulfate, filtered and concentrated. The resulting residue was subjected to flash column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether to afford the alcohol **25** (1.31 g, 100% yield): ir 3320 cm^{-1} (hydroxy); The ^1H nmr spectrum exhibited two sets of signals. The following data were attributed to the major isomer: δ4.74 (br, s, 2H, =C**H**$_2$), 4.02 (br, s, 1H, -C**H**(OH)-), 5.58 (m, 1H, -C**H**=), 1.76 and 1.80 (br, s, total 6H, 2x -C**H**$_3$). The following data were attributed to the minor isomer: δ4.74 (br, s, 2H, =C**H**$_2$), 4.18 (br, s, 1H, -C**H**(OH)-), 5.40 (m, 1H, -C**H**=), 1.76 and 1.80 (br, s, total 6H, 2x -C**H**$_3$); ms M^+ 152.1202 (calcd. for $C_{10}H_{16}O$: 152.1201).

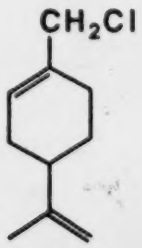
Carvone (24)



24

To a solution of phenyl dichlorophosphate (0.45 mL, 3 mmol) in freshly distilled dichloromethane (3 mL) at -10°C under an argon atmosphere, was added dimethyl sulfoxide (0.35 mL, 5 mmol) in dry dichloromethane (3 mL). After stirring for 2 min, triethylamine (0.70 mL, 5 mmol) was added dropwise followed by a solution of carveol (**25**) (152 mg, 1 mmol) in dichloromethane (2 mL). The reaction mixture was stirred for 5 min at -10°C and then allowed to warm up slowly to room temperature. After stirring for 45 min, water (10 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The combined organic solution was washed with saturated soldium chloride solution (20 mL), dried with magnesium sulfate, filtered and concentrated. The resulting residue was chromatographed on silica gel. Elution with 25% diethyl ether in petroleum ether gave the carbonyl compound **24** (122 mg, 81% yield): ir 1673 cm^{-1} (conjugated enone); ^1H nmr δ6.75 (m, 1H, =C**H**-), 4.75 (br, s, 1H, =C**H**H), 4.82 (br, s, 1H, =CH**H**), 1.80 (br, s, 3H, -C**H**$_3$) and 1.75 (br, s, 3H, -C**H**$_3$); ms M^+ 150.1042 (calcd. for $C_{10}H_{14}O$: 150.1045).

1-Chloromethyl-4-isopropenylcyclohexene (28)



28

(*a*) Using $PhOPOCl_2$ / Dimethyl sulfoxide

To a solution of phenyl dichlorophosphate (3.0 mL, 20 mmol) in dry dichloromethane (5 mL) at -20°C under an argon atmosphere, were added sequentially with stirring, dimethyl sulfoxide (2.85 mL, 40 mmol) and β-pinene (**27**) (1.6 mL, 10 mmol). The reaction mixture was stirred for 5 min at -20°C and then allowed to warm up slowly to room temperature. After 20 min, water was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x30 mL). The combined organic solutions were dried with magnesium sulfate, filtered and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with 5% diethyl ether in petroleum ether to afford the chloride **28** (1.64 g, 95%): ir 3020 cm^{-1} (=CH); ^1H nmr δ5.85 (br, s, 1H, =C**H**-), 4.75 (m, 2H, =C$\mathbf{H}_2$), 4.05 (s, 2H, -C$\mathbf{H}_2$Cl), 2.20 (m, 4H, -C$\mathbf{H}_2$C$\mathbf{H}_2$-) and 1.75 (br, s, 3H, -C$\mathbf{H}_3$); ms M^+ 170.0863 and 170.0838 (calcd. for $C_{10}H_{15}Cl$: 170.0864 and 172.0834).

(*b*) Using $POCl_3$ / Dimethyl sulfoxide

Dimethyl sulfoxide (0.14 mL, 2 mmol) was added to a solution of phosphorus oxychloride (0.10 mL, 1 mmol) in dry dichloromethane (3 mL) at -20°C. After stirring for 5 min at -20°C, β-pinene (**27**) (0.16 mL, 1 mmol) was introduced. The reaction mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After an hour, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x25 mL). The organic solution was dried

over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% diethyl ether in petroleum ether gave the chloride **28** (169 mg, 100% yield). The ir, ^1H nmr and mass spectra were identical to those reported previously (*vide supra*).

References

1. Reviews: W.W. Epstein and F.W. Sweat, *Chem. Rev.*, **67**, 247 (1967); T. Durst, *Adv. Org. Chem.*, **6**, 285 (1969); J.G. Moffatt in "Oxidation", Vol. 2, R.L. Augustine and D.J. Trecker, Ed., Marcel Dekker, New York, N.Y., 1971.

2. N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).

3. N. Kornblum, W. J. Jones and G. J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959).

4. A. J. Mancuso and D. Swern, *Synthesis*, 165 (1981).

5. K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661, 5670 (1965).

6. (a) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965); (b) J. D. Albright and L. Goldman, *ibid.*, **89**, 2416 (1967).

7. J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965).

8. S. M. Ifzal and D. A. Wilson, *Tetrahedron Lett.*, 1577 (1967).

9. K. Omura, A. K. Sherma and D. Swern, *J. Org. Chem.*, **41**, 957 (1976).

10. A. K. Sharma and D. Swern, *Tetrahedron Lett.*, 1503 (1974); (b) A. K. Sharma, T. Ku, A. D. Dawson and D. Swern, *J. Org. Chem.*, **40**, 2758 (1975).

11. S. L. Huang, K. Omura and D. Swern, *Synthesis*, 297 (1978).

12. A. G. Mancuso, S. L. Huang and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978).

13. K. Omura and D. Swern, *Tetrahedron*, **34**, 1651 (1978).

14. A. B. Smith,III, T. L. Leenay, H. J. Liu, L. A. K. Nelson and R. G. Ball, *Tetrahedron Lett.*, **29**, 49 (1988).

15. E. J. Corey and C. U. Kim, *Tetrahedron Lett.*, 919 (1973).

16. J. D. Albright, *J. Org. Chem.*, **39**, 1977 (1974).

17. J. B. Hendrickson and S. M. Schwartzman, *Tetrahedron Lett.*, 273 (1975).

18. T. E. Varkey, G. F. Whitfield and D. Swern, *J. Org. Chem.*, **39**, 3365 (1974).

19. S. S. Rawalay and H. J. Schechter, *J. Org. Chem.*, **32**, 3129 (1967).

20. F. F. Stephens and J. D. Bower, *J. Chem. Soc.*, 2971 (1949).

21. K. Nakagawa, H. Onoue and T. Sugita, *Chem. Pharm. Bull.*, **12**, 1135 (1964).

22. (a) W. E. Bachmann, M. P. Cava and A. S. Drieding, *J. Am. Chem. Soc.*, **76**, 5554 (1954); (b) A. I. Scott and T. J. Wilkinson, *Synth. Commun.*, **10**, 127 (1980).

23. B. M. Trost and G. Liu, *J. Org. Chem.*, **46**, 4617 (1981).

24. E. J. Corey and K. Achiwa, *J. Am. Chem. Soc.*, **91**, 1429 (1969).

25. J. H. Babler and B. J. Invergo, *J. Org. Chem.*, **46**, 1937 (1981).

26. H. Rapoport and T. F. Buckley, *J. Am. Chem. Soc.*, **104**, 4446 (1982).

27. (a) E. E. Snell and S.J. DiMari, *Enzymes*, **2**, 335 (1970); (b) H. C. Dunathan, *Adv. Enzymol. Relat. Areas Mol. Bio.*, **35**, 79 (1971); (c) L. Davis and D. E. Metzler, *Enzymes*, **7**, 33 (1972); (d) D. E. Metzler, *Adv. Enzymol. Relat. Areas Mol. Bio.*, **50**, 1 (1979).

28. E. J. Corey, C. U. Kim and M. Takeda, *Tetrahedron Lett.*, 4339 (1972).

29. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley and Sons Inc., New York, 1967.

30. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

31. E. Kuhle, *Synthesis*, 561 (1971).

32. L. Rasteikiene, D. Greiciute, M. G. Lin'kova and I. L. Kuunyants, *Russian Chem. Rev.*, **46**, 548 (1977).

33. H. Lecher, F. Holschneider, K. Koberle, W. Speer and P. Stocklin, *Chem. Ber* , **58**, 409 (1925).

34. B. Rathke, *Chem. Ber.*, **3**, 858 (1870).

35. W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, **90**, 2075 (1968).

36. N. Kharasch and C. M. Buess, *J. Am. Chem. Soc.*, **72**, 3529 (1950).

37. N. Kharasch and C. M. Buess, *J. Am. Chem. Soc.*, **71**, 2724 (1949).

38. N. Kharasch, C. M. Buess and W. King, *J. Am. Chem. Soc.*,**75**, 6035 (1953).

39. H. Kwart and E. N. Givens, *J. Am. Chem. Soc.*, **90**, 378, 386 (1968).

40. N. Isenberg and M. Grdinic, *J. Chem. Educ.*, **46**, 601 (1969).

41. R. C. Fuson, C. C. Price and D. M. Burness, *J. Org. Chem.*, **11**, 475 (1946).

42. H. Brintzinger, K. Pfannstiel, H. Kodadebisch and K. E. Kling, *Chem. Ber.*, **83**, 87 (1950).

43. E. Schneider, *Chem. Ber.*, **84**, 911 (1951).

44. K. R. Brower and I. B. Douglas, *J. Am. Chem. Soc.*, **73**, 5787 (1951).

45. H. Lecher and F. Holschneider, *Chem. Ber.*, **57**, 755 (1924).

46. T. Zincke, *Chem. Ber.*, **44**, 769 (1911).

47 H. Bohme and H. J. Gran, *Liebigs Ann. Chem.*, **577**, 68 (1952).

48. H. J. Liu and J. M. Nyangulu, *Tetrahedron Lett.*, **29**, 3167 (1988).

49. M. Windholz, S. Budavari, R. F. Blumetti and E. S. Otterbein, "The Merck Index", 10th Ed. Merck and Co. Inc., Rahway N.J., 1983, Entry 1856.

50. A. B. Booth and E. A. Klein, *U. S. Pat.* 2796428 (1957).

51. G. O. Uboergo, G. Malimskas and H. A. Taher, *Essenze Deriv. Agrum.*, **56**, 33 (1986).

52. T. Suga, *Bull. Chem. Soc. Japan*, **31**, 569 (1958).

53. I. Fleming and I. Paterson, *Synthesis*, 736 (1979).

54. E. E. Royals and S. E. Horne, Jr., *J. Am. Chem. Soc.*, **73**, 5856 (1951).